Systematic Review in Exposure Science Summit

Thursday, April 25th, 2019

Hosted by
EPA/ORD/NCEA

Systematic Review in Exposure Science Summit
• Discussion Questions •

What advances are needed in IT tools and databases to identify, capture, and share exposure science data?

What systematic review methods and approaches are of interest to the federal exposure science community and/or might advance your Agency's current practices?

Questions

What applications of SR discussed today might be relevant or informative to your Agency's current or future uses? Where can we build bridges to communicate and collaborate with offices using similar applications?

Was there anything that we did not discuss today that you would like to bring up for discussion today and/or follow up on in the future?

Systematic Reviews: Traditional and Targeted Approaches

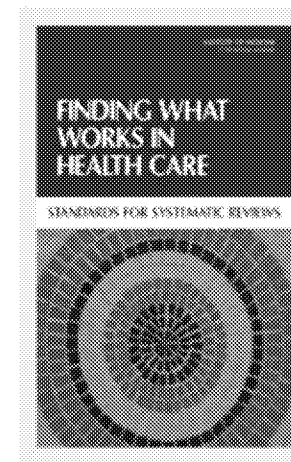*Systematic Review in Exposure Science Summit*
Andrew Kraft
IRIS Associate Director for Science, EPA-ORD
April 25th, 2019

Disclaimer: The views expressed in this presentation are those of the author and do not necessarily represent the views or policies of the U.S. EPA

A structured and documented process for transparent literature review[1]

"As defined by IOM [Institute of Medicine], systematic review 'is a scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies.'" (NRC, 2014)
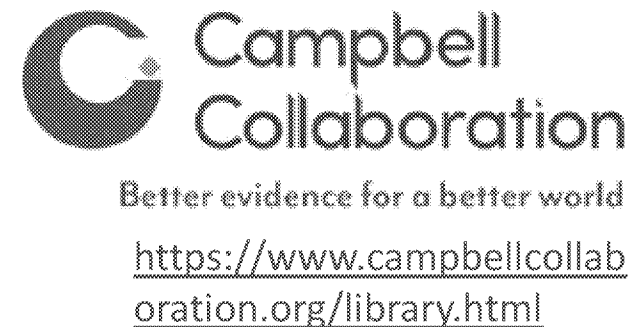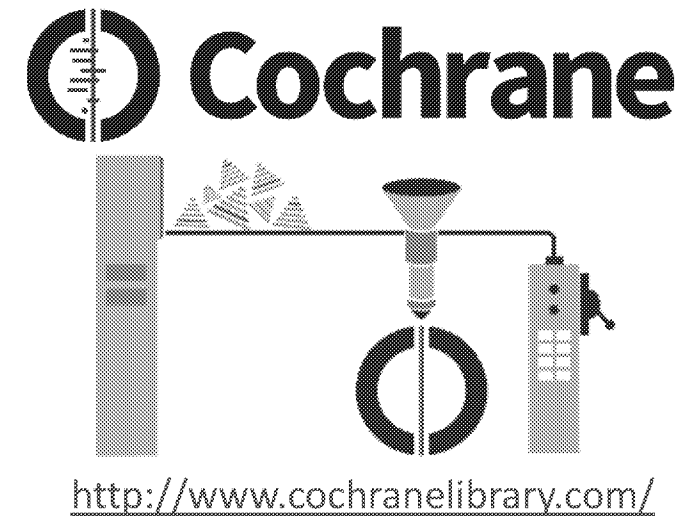
"The output of a systematic review can be "narrative" (structured review and summary of the available data), "qualitative" (non-numerical conclusions, including conceptual frameworks), or "quantitative" (meta-analysis or meta-regression)." (Deeks et al., 2011 [Cochrane Collaboration])

[1] Institute of Medicine. Finding What works in Health Care: Standards for Systematic Reviews. p.13-34. The National Academies Press. Washington, D.C. 2011

4

- Initially developed for evidence-based medicine (clinical trials)
  - **Cochrane:** a non-profit founded 1993 to conduct & share health intervention systematic reviews

- Growing importance for

- Public health

- Social interventions

- Economic evaluations

- **Environmental science and toxicology**

  - Ecological impacts

  - Human health hazards

  - Exposure

http://www.cochranelibrary.com/

Campbell Collaboration

Better evidence for a better world

https://www.campbellcollaboration.org/library.html

Collaboration for Environmental Evidence

http://www.environmentalevidence.org/

*Slide from: EPA SR CoP SharePoint Site
See site for additional background materials

5

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- **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)** (http://www.prisma-statement.org/)
  - "Evidence-based minimum set of items for reporting in systematic review and meta-analyses"... The "classic" checklist.
  - Word-based form focuses on reports evaluating randomized trials, but can be applied to other review types

- **RepOrting standards for Systematic Evidence Syntheses (ROSES)** (https://www.roses-reporting.com/)
  - "Preparation of systematic review and map protocols and final reports... details that should be reported"
  - Multiple forms available (excel-based):
    - Systematic review protocols and Systematic review reports
    - Systematic map protocols and Systematic map reports
    - Literature flow diagrams
  - Extracts information similar to above, with mandatory and optional steps, with modifications such as:
    - Type of review
    - Deviations from protocol, with justifications
    - Flexibility in method used for critical appraisal of study validity and how this will be used in the evidence synthesis
    - Tracks author responsibilities, search update procedures, stakeholder engagement, effect modifiers, type of evidence synthesis, and estimated comprehensiveness of the review

6

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Step of Systematic Review	In Systematic Map*	Notes
1. Objectives and Rationale	√	Based on Scoping within EPA
2. Publicly Available Protocol	√	
3. Search Strategy	√	
4. Study Screening, based on PI/ECO	√	Populations, Exposure, Comparators, Outcomes Prisma: "I" for "Intervention"
5. Data Collection	√	ROSES: included after step #6
6. Evaluation of Study Validity*		
7. Summary of Results	√	
8. Evidence Synthesis/Integration and Other Analyses Across Studies		IRIS separates synthesis from integration (or WOE)
9. Summary Conclusions (qualitative or quantitative) and Limitations (i.e., of the review; of the evidence		May be qualitative or quantitative; limitations of both the review and evidence base

* in IRIS we have been including some components of #6 in our evidence mapping
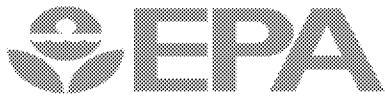
- "systematic reviews are not limited to a particular scope" (Deeks et al., 2011 [Cochrane])

- Reviewers are often "challenged with integrating the results from a broad and heterogenous evidence base" (Whaley et al., 2016 [Environment International])

Scope of Review - broad versus targeted systematic review, systematic map, or rapid review, determined by:

- Decision Context (e.g., immediacy of need; prioritization versus rulemaking)

- Availability of well-conducted Systematic Reviews or Systematic Maps

- Resource Constraints

- Database Composition. For example, for environmental health:

  - *Clinical and Preclinical Medicine*- Narrow PECO: defined effect [I.Q. change] in a defined population [children aged 6-9] receiving a defined intervention and dosage, typically with a pre-specified frequency and duration. Scope: 5-15 studies (generally 10s of homogeneous data points)

  - *Traditional Review*- Broad PECO(s): any effect in any population exposed to any level of the agent with any frequency for any duration. Scope: 20-100 studies (generally 100s of heterogeneous data points)

  - *Non-Traditional Review (e.g., Prioritization)*- Variable PECO(s): depends on the type and quantity of data available, and intended use. Scope: 2-1000$^+$ studies (can be 1000s of heterogeneous data points)

8

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	Pharmaceutical	Pesticide	Criteria air pollutant	Environmental chemical (typical)	Environmental chemical (data poor)
Randomized control trials	Required	--	--	--	--
Guideline animal studies	Required	Required	Sometimes	Sometimes	--
Observational epidemiology studies (typically long-term)	Yes	Sometimes	Yes	Sometimes	--
Other medium- or long-term animal studies	Yes	Yes	Yes	Yes	--
Acute exposure (human cases or volunteers; animal toxicity)	Yes	Yes	Yes	Yes	Sometimes
Mechanistic studies (in vitro; molecular screens)	-	Sometimes	-	Yes	Sometimes
Read-across or similar	-	-	-	-	Yes

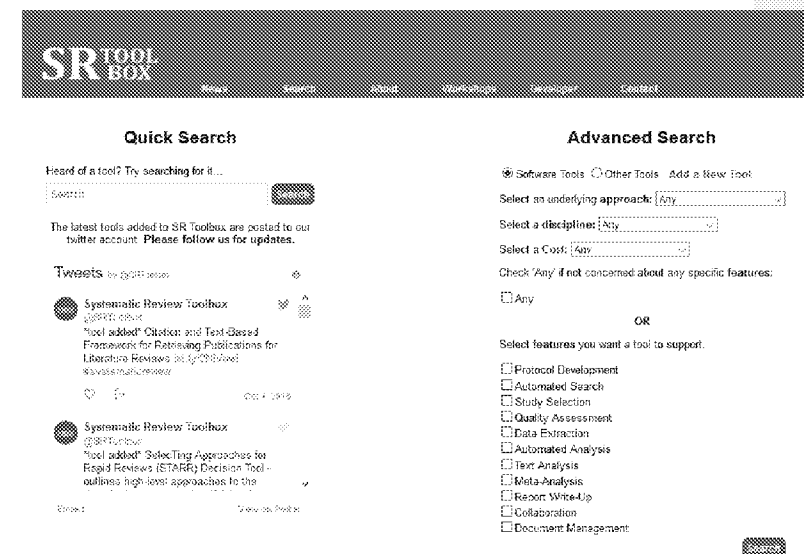-- Generally unavailable   - Often available, but generally not used in assessments supporting decision- making

9

Useful to develop standardized procedures and considerations for each step

Review Initiated → Draft Developed

Scoping
Systematic Review Protocol
Literature Inventory
Study Evaluation
Data Extraction
Evidence Integration
Derive Toxicity Values

Problem Formulation
Literature Search
Refined Analysis Plan
Organize Hazard Review
Evidence Analysis and Synthesis
Select and Model Studies

Scoping and P.F. determine what each review covers

Protocols document how each review will be conducted

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- Exponential growth of tools

- Validation efforts often limited to traditional systematic review topics

- Applicability to more heterogeneous evidence bases remains unclear

- Need for fit-for-purpose application through demonstration (case studies)

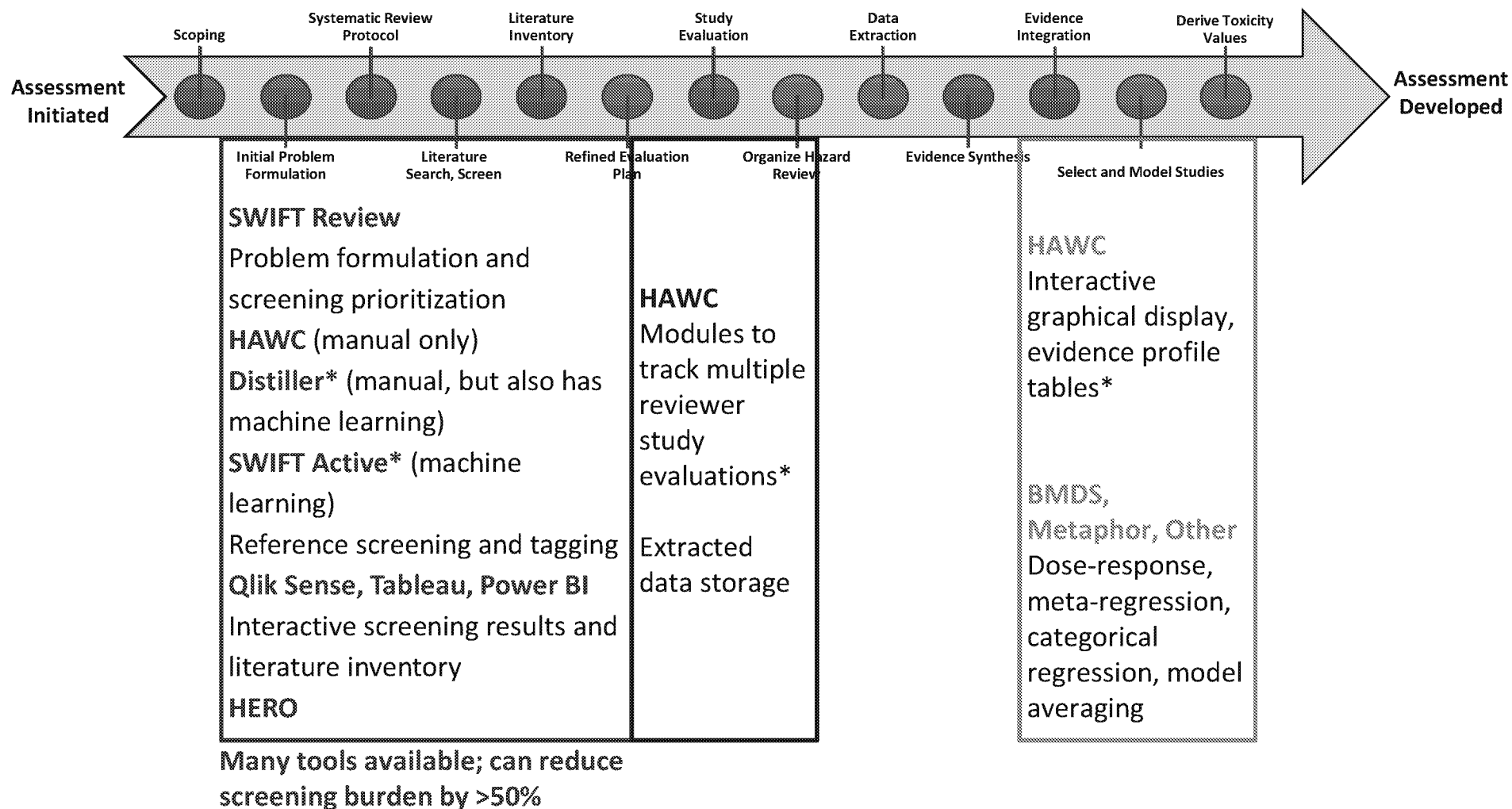- Collaborative testing is underway for diverse data sources...
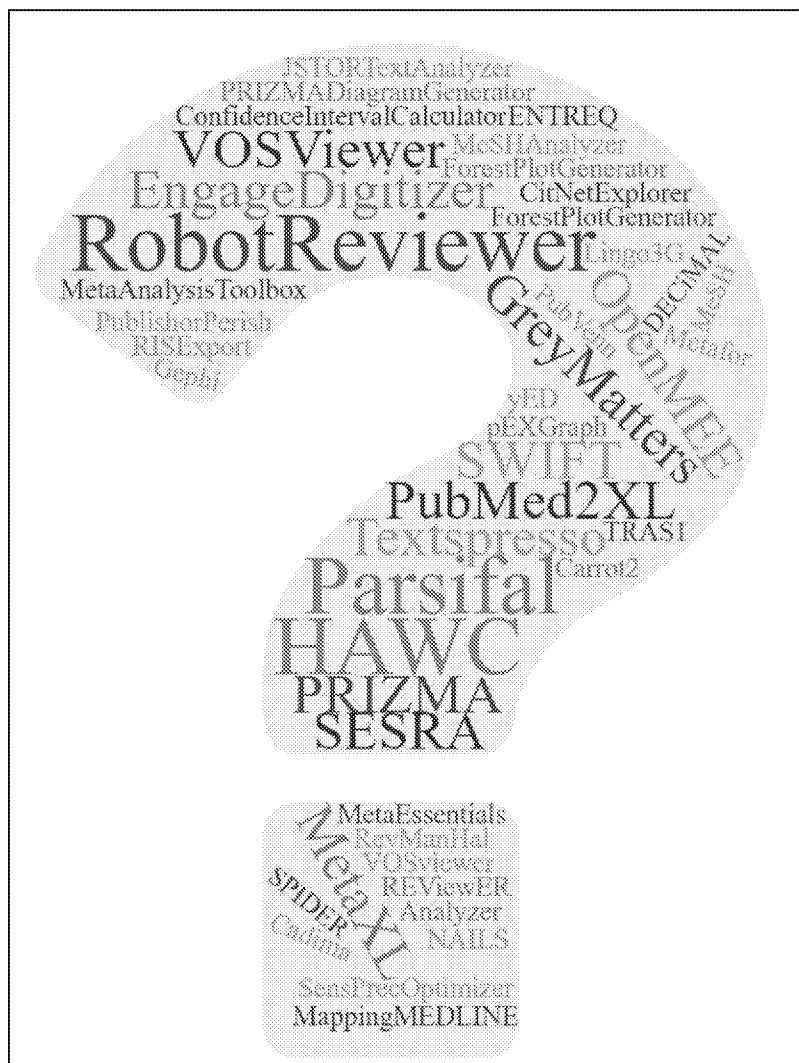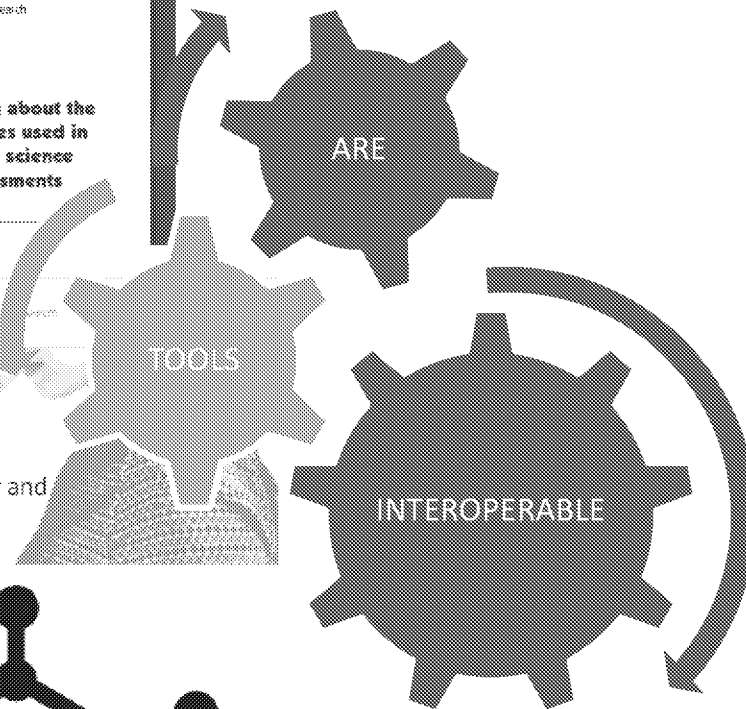

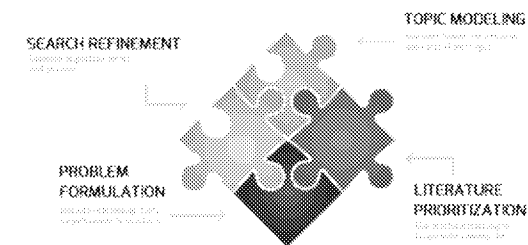wordclouds.com

systematicreviewtools.com

Assessment Initiated → Scoping · Systematic Review Protocol · Literature Inventory · Study Evaluation · Data Extraction · Evidence Integration · Derive Toxicity Values → **Assessment Developed**

Initial Problem Formulation · Literature Search, Screen · Refined Evaluation Plan · Organize Hazard Review · Evidence Synthesis · Select and Model Studies

SWIFT Review
Problem formulation and screening prioritization
HAWC (manual only)
Distiller* (manual, but also has machine learning)
SWIFT Active* (machine learning)
Reference screening and tagging
Qlik Sense, Tableau, Power BI
Interactive screening results and literature inventory
HERO

Many tools available; can reduce screening burden by >50%

HAWC
Modules to track multiple reviewer study evaluations*

Extracted data storage

HAWC
Interactive graphical display, evidence profile tables*

BMDS, Metaphor, Other
Dose-response, meta-regression, categorical regression, model averaging

supports (or will support) multiple evaluators and tracking

12

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- **Cochrane Collaboration:** https://www.cochrane.org/
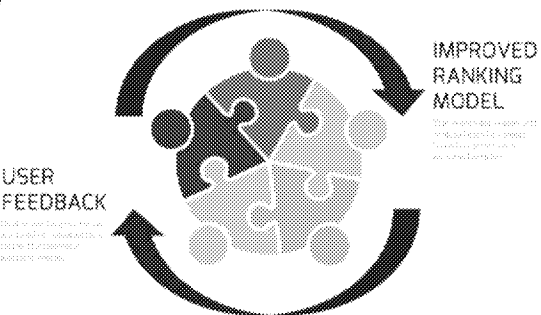
  – Probably the most well-recognized international name in systematic review; primary focus on controlled trials
  – Reviews are developed within Cochrane
  – Protocols are peer-reviewed and published

  [Learning resources and software tools (e.g., Covidence; RevMan) for developing Cochrane reviews are provided on the website]

- **Prospero:** https://www.crd.york.ac.uk/prospero/

  – International, public registry of protocols for a variety of topics
  – Allows for comparison of completed review with protocol planned at inception

- **Campbell Collaboration:** https://www.campbellcollaboration.org/

  – International repository of protocols and reviews developed following standardized templates and procedures
  – Protocols undergo review by editors, a content expert, and a methods expert, and are published

- **Considerations for Tailored or Targeted Approaches**

  – *Generally expected for all formal systematic reviews*
  – As implemented in IRIS, protocols are posted when reviews are expected to contain formal conclusions (document decision rationale)
     - Thus, most systematic evidence maps would not include a protocol, whereas most "updates" would
  – Protocol should describe and justify any tailored focus (e.g., to particular populations, routes or exposure level ranges, or outcomes)

14

Best Practices for Literature Searches (IRIS Tools: HERO)**:**

- Include multiple electronic databases relevant to the topic area of the review
- *Include methods for identifying "gray literature", such as unpublished research reports*
- *Involve an information specialist in the design of the search strategy*
- Document search strings, search dates, and process for regularly updating the literature search
- Include methods for identifying missed studies (e.g., public input; comparison to references in other [systematic] reviews; review studies citing those identified as relevant to the review)

Considerations for Tailored or Targeted Approaches

- Scope of the literature search(es) (targeted focus) should be defined based on the research objectives, e.g.,
  - Conducting multiple health effect-specific searches rather than a comprehensive search
  - Limiting search to studies in particular species or relevant to a subset of potential human exposure scenarios
- Consider the utility of adopting and updating literature searches in other, similarly scoped systematic reviews
  - Requires consideration of the rigor and comprehensiveness of the prior search

15

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- **Best Practices for Literature Screening** (IRIS Tools: Distiller; SWIFT Review and Active; Tableau; HERO):

  - *Use two, independent screeners with a process for conflict resolution*
  - Validate and pilot-test (Note: useful to capture basic study characteristics during, or subsequent to, screening; next slide)
  - *Document screening decisions (e.g., use of "tags"; literature flow diagrams)*
  - PECO criteria are typically used for screening decisions; handling of non-PECO studies should be described
  - Study quality considerations should not be used as screening criteria for relevance
    - Could include as a "first-pass", preliminary study evaluation consideration

- **Considerations for Tailored or Targeted Approaches**

  - Machine learning-based approaches are often useful for large databases
    - Should document the anticipated comprehensiveness of the strategy (e.g., SWIFT approximates a % studies identified)
  - Consider utility of adopting and updating literature identified as relevant in other, similarly scoped systematic reviews
    - Requires consideration of the rigor and comprehensiveness of the prior search and screening process

- **Today's Relevant Topics:** Amina Wilkins (ORD-NCEA)- SWIFT Review and Tableau; Lyle Burgoon (USACE)- use of AI for screening; Kellie Fay (OCSPP-OPPT)- Bioportal ontology lookup tool; Ashlee Aldridge (OCSPP-OPP)- Use of Endnote to identify key epidemiology studies; Linda Phillips (ORD-NCEA)- S.R. for updating the PCB exposure estimation tool

16
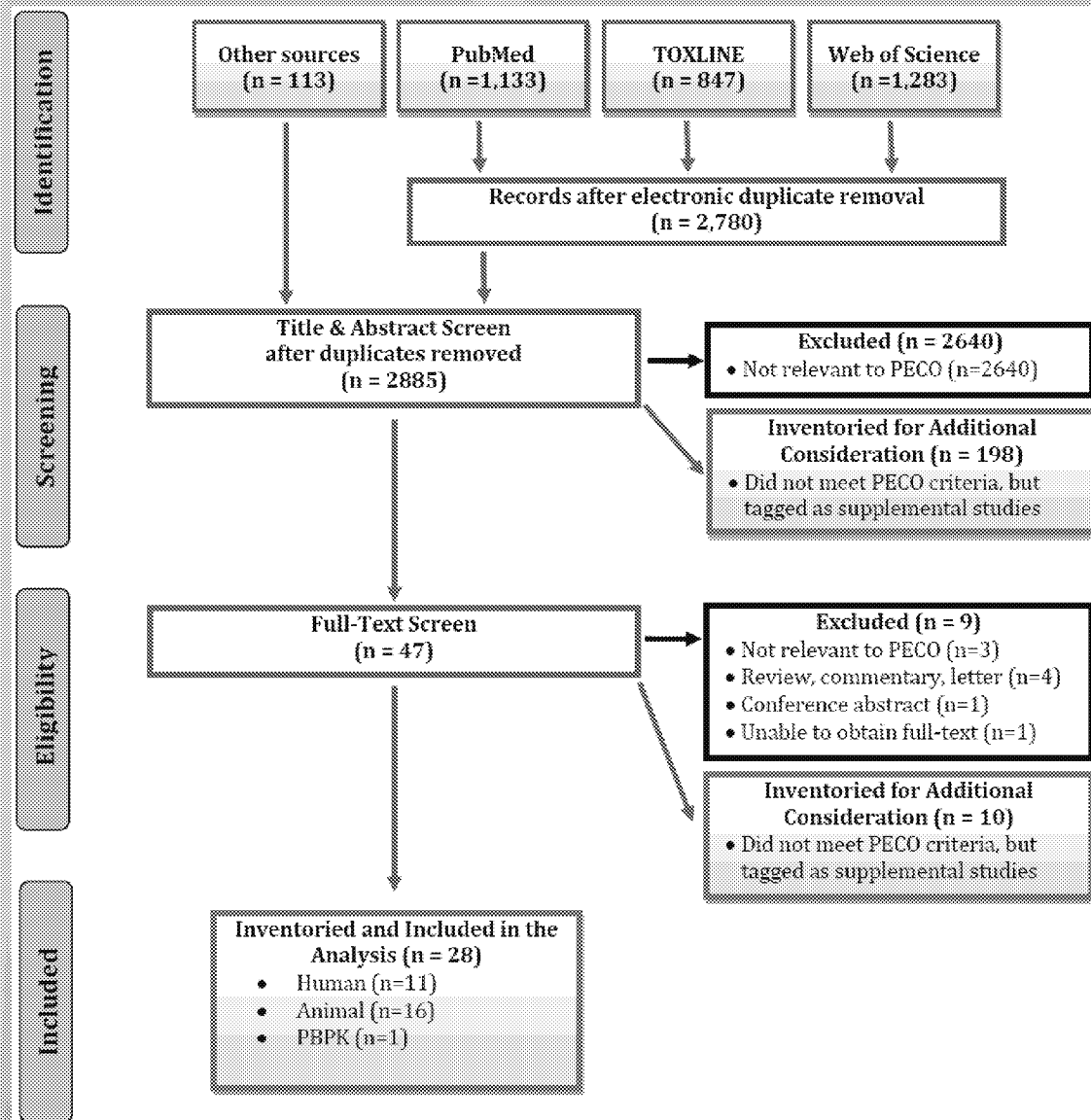
- **Documents results and rationale**

- **HERO can be used to share repositories of included, excluded, and supplemental studies**

Example modeled on the draft chloroform protocol (2018)

17

SUBMIT FORM and go to [▾] or Skip to Next

Forms Independently Entered by 2 Reviewers

1. **Based on Title and Abstract does the article contain relevant human, animal, or in vitro evidence?**

   ◯ Yes   ◯ No   ⦿ No, but has supportive information
   ◯ Unclear (e.g., no abstract)   Clear Response

2. **What kind of evidence or supportive information?**

   ☐ human

   ☐ animal

   ☑ in vitro, omics, alternative model systems

3. **What kind of supportive information?**

   ☑ MOA/mech (cancer)

   ☐ MOA/mech (non-cancer)

   ☐ case report or poisoning

   ☐ non-inhalation route

   ☐ mixture

   ☐ ADME/PBPK

   ☐ exposure assessment

   ☐ THM, disinfection/chlorination by-product, swimming pools

   ☐ susceptible population

   ☐ anesthesia/inhalent

P — **Human:** Any population and life stage (occupational or general population, including children and other sensitive population). The following study designs will be considered most informative: controlled exposure, cohort, case-control, cross-sectional, and ecological. Note: Case reports and case series will be tracked during study screening, but are not the primary focus of this assessment. They may be retrieved for full-text review and subsequent evidence synthesis if no or few informative study designs are available. Case reports can also be used as supportive information to establish biologic plausibility for some target organs and health outcomes.
Animal: Nonhuman mammalian animal species (whole organism) of any life stage (including preconception, in utero, lactation, peripubertal, and adult stages).

E — **Human:** Any exposure to chloroform, including occupational exposures, via inhalation. Exposures quantified by either actual exposure measurements or occupational exposure history are preferred. Studies of chloroform in the context of its use as an anesthetic gas will be excluded.
Animal: Any exposure to chloroform via inhalation. Studies employing chronic exposures or short-term, developmental-only exposures will be considered the most informative. Studies involving exposures to mixtures will be included only if they include an arm with exposure to chloroform alone. Studies utilizing chloroform as an extraction solvent to isolate specific chemical constituents will be excluded.
PBPK: Studies describing physiologically-based pharmacokinetic (PBPK) models for chloroform will be included.

C — **Human:** A comparison or reference population exposed to lower levels (or no exposure/exposure below detection limits) of chloroform, or exposed to chloroform for shorter periods of time.
Animal: A concurrent control group exposed to vehicle-only treatment.

O — All health outcomes (both cancer and noncancer). In general, endpoints related to clinical diagnostic criteria, disease outcomes, histopathological examination, or other apical/phenotypic outcomes will be prioritized for evidence synthesis over outcomes such as biochemical measures. As discussed above, based on preliminary screening work, EPA anticipates that a systematic review for health effect categories other than those identified (i.e., nasal cavity effects, nervous system effects, liver and kidney effects, immunotoxic effects, and reproductive/developmental effects) will not be undertaken unless a significant amount of new evidence is found upon review of references during the comprehensive literature search.

SUBMIT FORM and go to [▾] Skip to Next   **Example Distiller form (chloroform PECO)**

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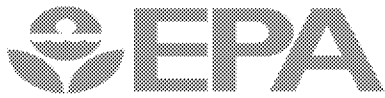
- **Best Practices for Study Evaluation in Systematic Reviews** (IRIS Tools- HAWC):
  - _Should address internal validity (How reliable are the results?)_, aka "risk of bias" (RoB). Some approaches go beyond RoB.
  - When possible, use 2 independent, topic-specific experts and a process for conflict resolution and decision documentation.
  - Most commonly this is done in an outcome-specific manner (outcome-specific considerations may be developed, if needed)
  - Expert judgment is an intrinsic part of study evaluation; thus, use of topic-specific experts is preferred.
  - _Results of the individual study reviews should influence evidence synthesis decisions_; the protocol should describe 'how'
  - NAS (2014): "EPA should select a method that is transparent, reproducible, and scientifically defensible. Whenever possible, there should be empirical evidence that the methodologic characteristics that are being assessed in the IRIS protocol have systematic effects on the direction or magnitude of the outcome...for each type of study design in each data stream."
- **Considerations for Tailored or Targeted Approaches**
  - It may be possible to prioritize studies for individual-level review (e.g., by study design or testing of specific endpoints). In these cases, it may be decided that sufficient data to draw conclusions can be reached w/o non-prioritized studies
    - Any such decisions should be tracked as a revision to the protocol
  - For some applications (e.g., evidence mapping), a subset of the study evaluation criteria may be applied as a first-pass tool
    - Considerations applied as a first-pass should generally be highly impactful to the overall review (typically on exposure)
- **Today's Relevant Topics:** Becky Nachman (ORD-NCEA)- IRIS Epidemiology study evaluation; Eva Wong (OCSPP-OPPT)- TSCA exposure assessment; Michael Breen (ORD-NERL)- future directions for epidemiology exposure assessment in air pollution

19

EPA-IRIS

NTP-OHAT

SciRAP

NavGuide

EPA-TSCA

NTP-ORoC

ROBINS-I

ToxRTool

**EFSA**
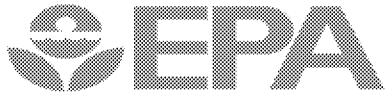
- **Best Practices for Data Extraction** (IRIS Tools- HAWC; BMDS; R; GraphPad Prism; TableBuilder; most do not talk to HAWC)**:**
  - *Include a QA process* (e.g., one reviewer entry and independent verification). Tools should allow QA'd data to be 'locked'.
  - Apply consistent terminology (across review products; across centers conducting similar reviews; next slide)
  - It often makes sense to copy and paste basic methods text from the study to avoid errors and interpretation
  - Transformed data and other information not included in the publication should be tracked and publicly accessible
  - Reviewer and author judgments should be clearly identified as such (e.g., N/LOAEL calls), with explanations
  - *Visualizations should support the evidence synthesis*, and allow for evaluation of study heterogeneity on a given topic

- **Considerations for Tailored or Targeted Approaches**
  - In some cases, full extraction of study data is not efficient ('extraction lite' is preferred). Similarly, detailed tables and graphics might be included for only a subset of topic areas (e.g., health hazards for which a conclusion will be drawn).
    - Consider the types of study designs, outcomes, etc. are likely to be emphasized in the review.
  - Although currently uncommon, future efforts to share QA'd data across overlapping reviews could reduce redundancy

- **Today's Relevant Presentations:** Cathy Fehrenbacher (OCSPP-OPPT)- Effective data extraction and use of outside expertise; Ed Perkins (USACE)- Cross-agency collaboration opportunities and communication challenges; Kate Schofield (ORD-NCEA)- The Ecological Evidence Exchange; Andy Rooney (NTP)- Machine learning and automation to address assessment challenges

21
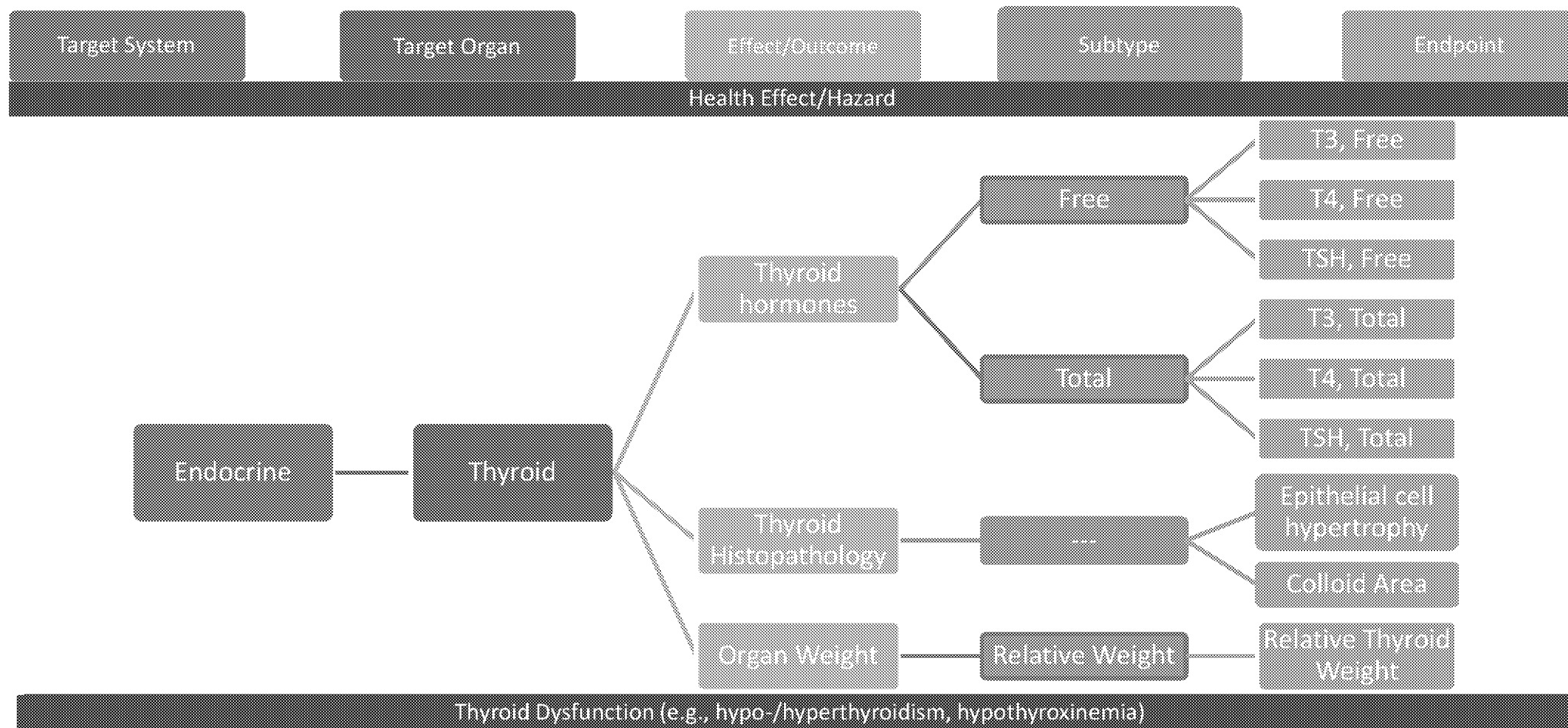
- **Best Practices for Evidence Synthesis and Drawing Conclusions** (IRIS Tools- HAWC; Metafor):

  - *The evidence synthesis should probe and investigate potential explanations for heterogeneity across studies*
  - When calculating estimates across studies (e.g., a meta-analysis), it is preferable to do so de novo, rather than relying on existing estimates, primarily due to the need to document and justify all decision steps.
    - However, it can be useful to review such analyses for relevant studies and considerations
  - *The conclusion(s) from the review should be succinct, clear, and well-supported*. There should be a transparent rationale for all decisions, and any significant uncertainties (in both the review and the evidence base) should be described. Quantitative summaries should include both the point estimate and confidence interval.
  - Frameworks exist for drawing transparent expert conclusions for a body of evidence, e.g.,: GRADE; EPA-IRIS; NTP-OHAT

- **Considerations for Tailored or Targeted Approaches**

  - For conclusions on which a clear scientific consensus exist, consider starting from that conclusion as a baseline
    - E.g., it is known that methylmercury causes CNS effects, so review focus is on studies informing dose-response
  - A conclusion(s) from a systematic review exists that could be similarly incorporated as a starting place
    - The rigor, reporting, and comprehensiveness of the review should be evaluated
      - Tools exist to evaluate existing systematic reviews, e.g.,: AMSTAR checklist; CASP checklist; Joanna Briggs Institute

- **Today's Relevant Topics:** Jeanette Reyes (ORD-NCEA)- ISAs exposure assessment; Micah Bennett (ORD-NCEA)- nutrient-stressor response; Jessica Frank (ORD-NERL)- lead exposure assessment; Andy Rooney (NTP)- OHAT evidence integration

23

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Studies and interpretation	Factors that increase strength	Factors that decrease strength	Summary of findings	Within stream evidence judgments	Inference across evidence streams	Overall conclusion
[Health Effect or Outcome Grouping]						

Evidence from Human Studies (Route)					• Human relevance of findings in animals
					 • Cross-stream coherence
					 • Other inferences:
					   ○ Information on susceptibility
					   ○ MOA analysis inferences
					   ○ Relevant information from other sources (e.g., read across)
						Describe conclusion(s) for the integration of all available evidence:
						
						 ⊕⊕⊕ Evidence demonstrates
						 ⊕⊕⊙ Evidence indicates
						 ⊕⊙⊙ Evidence suggests
						 ⊙⊙⊙ Evidence inadequate
						 − − − Strong evidence supports no effect

• References • Study confidence • Study design description	• Consistency • Dose-response gradient • Coherence of observed effects • Effect size • Mechanistic evidence providing plausibility • Medium or high confidence studies	• Unexplained inconsistency • Imprecision • Low confidence studies • Evidence demonstrating implausibility	• Results across studies • Human mechanistic evidence informing biological plausibility	Describe strength of the evidence from human studies, and primary basis: ⊕⊕⊕ Robust ⊕⊕⊙ Moderate ⊕⊙⊙ Slight ⊙⊙⊙ Indeterminate − − − Compelling evidence of no effect		
Evidence for an Effect in Animals (Route)						Summarize the models and range of dose levels upon which the conclusions were primarily reliant
• References • Study confidence • Study design description	• Consistency and/or Replication • Dose-response gradient • Coherence of observed effects • Effect size Mechanistic evidence providing plausibility • Medium or high confidence studies	• Unexplained inconsistency • Imprecision • Low confidence studies • Evidence demonstrating implausibility	• Results across studies • Animal mechanistic evidence informing biological plausibility	Describe strength of the evidence for an effect in animals, and primary basis: ⊕⊕⊕ Robust ⊕⊕⊙ Moderate ⊕⊙⊙ Slight ⊙⊙⊙ Indeterminate − − − Compelling evidence of no effect		

24

- **The principles of S.R. are applicable to all Environmental Health (EH) data**

- **Operationalizing S.R. for heterogeneous and oftentimes extensive EH evidence can be hard**

- **Case studies in application are needed to validate and refine tools for different applications**

- **Tools and approaches are needed to address aspects uncommon in clinical med. (e.g., exposure assessment)**

- **Reviews should be fit-for-purpose**

- **It is increasingly clear that collaboration is key (there are a lot of folks engaged on this topic)**
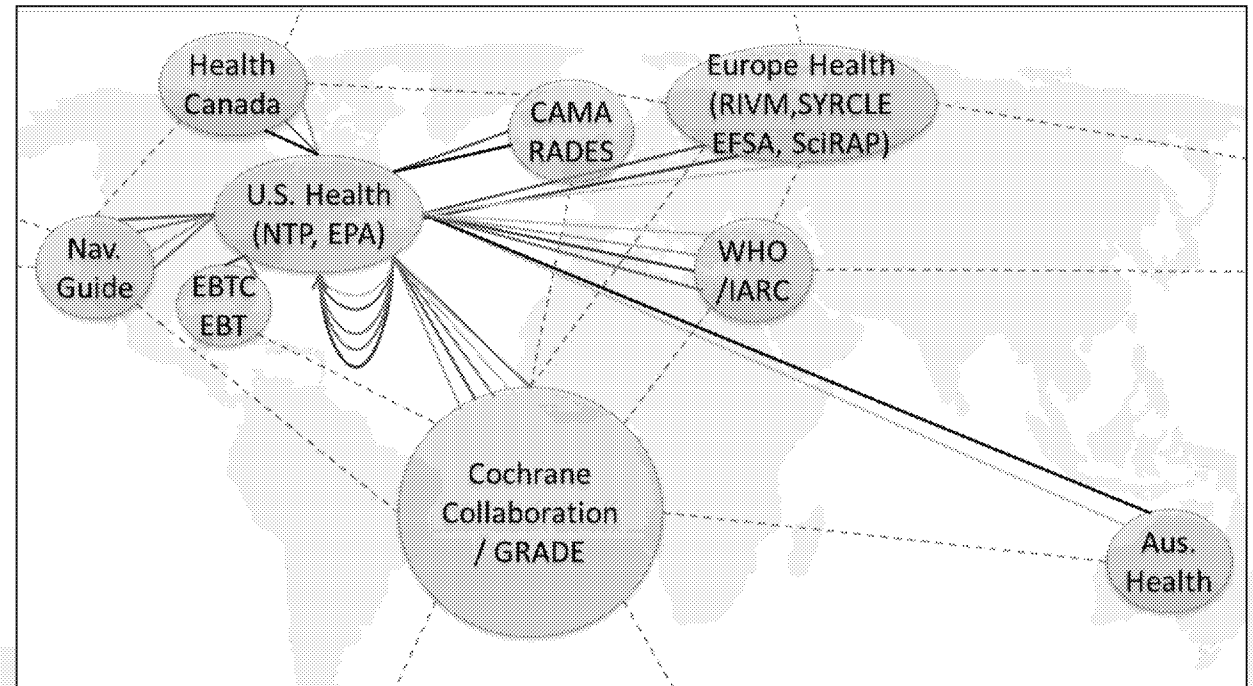
Acknowledgements

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Automation Tools

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IRIS
INTEGRATED RISK INFORMATION SYSTEM

Systematic Review in Exposure Science: Use of SR Tools in Developing Literature Search Strings to Identify Exposure Studies and Visualization of SR Data

Thursday, April 25, 2019

Amina Wilkins

U.S. EPA/ORD/NCEA/IRIS Program

"The findings and conclusions in this report (presentation) have not been formally disseminated by the U.S. EPA and should not be construed to represent any agency determination or policy."

- Difficult to identify studies with human exposure data
- Exposure and fate encompass a wide and diverse range of topics

- Goal: provide non-chemical specific search strings to identify exposure and fate records (can be used in PubMed, WoS, Toxline, etc.)

- Assembled a team of agency exposure & fate experts from various EPA program offices, including ORD & OCSPP
  - Working with a HERO library scientist
  - Assembling previously used search strings
  - Experts are providing sets of 'on-' and 'off-' topic references to HERO; and providing a list of relevant and prioritized keywords
  - HERO is iteratively testing search strings (trying to decide best approach; i.e., for Boolean terms OR term OR term vs. (term OR term) OR term; exploring use of HERO Classifier tool
  - Need to decide how granular to get with main and subcategories

Draft Exposure Categories and Sub-Categories

Sources, Production, Uses

Source

Production

Use

Emission

Formation

Release

Manufacture; industry

Populations with Potentially Greater Exposures

Occupational exposure

Infants; children

Native American; tribal

Highly exposed

Environmental Concentrations

Concentration

Media

  Air; atmospheric

  Dust

  Water

    Surface water

    Groundwater

    Effluent

  Soil

  Sediment

  Fish; shellfish

  Food

  Drinking water

  Consumer products

Potential for Human Exposure

Exposure; dose

  Ingestion; oral; consumption

  Dermal

  Inhalation

Contact

Body burden

Biomonitoring; biomarker

  Blood

  Serum

  Plasma

  Urine

  Cord blood

  Human milk; breast milk

Average daily dose; average daily intake

Environmental Fate and Transport

Persistence   Half life

Fate   Environmental media

Transport   Air

Adsorption   Water

Volatilization   Soil

Partitioning   Sediment

Photolysis   Aquatic organisms

Hydrolysis   Terrestrial organisms

Mobility

Bioconcentration; bioaccumulation;

Biomagnification; accumulation

Degradation

- Contract with Sciome, developers of SWIFT Review, to test the performance of the HERO search strings and make recommendations for improving the search
  - Identify relevant exposure references
  - Correctly tag or categorize references
  - Comparing search string results to human, manually screened data
- Sciome Workbench for Interactive computer-Facilitated Text-mining
- Free software program that assists with literature prioritization
- Search strings will be useful to SWIFT but **can also be used by anyone** to identify exposure and fate references
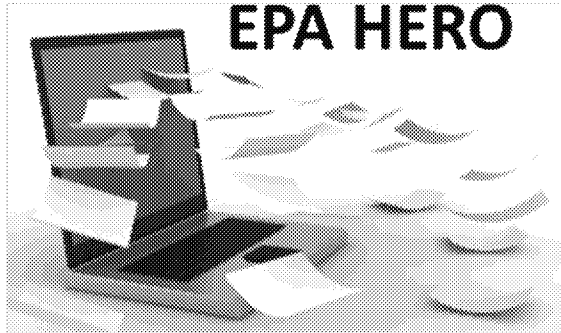
EPA HERO

Health & Environmental Research Online

- Literature searching
- Provide .RIS files
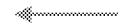
SWIFT REVIEW

- Landscaping
- Targeting

⌘ DistillerSR

- Screening
- Tagging

Landscaping

SWIFT REVIEW

Chemical A - Health Outcomes by Year

	2017-2018	2015-2016	2013-2014	2011-2012	2009-2010	2007-2008	2005-2006	Totals
Endocrine	31	261	310	304	328	315	311	1,860
Nutritional and Metabolic	34	185	210	178	191	190	208	1,196
Hematological and Immune	18	105	137	113	139	125	121	758
Hepatic	15	74	74	73	82	94	91	503
Developmental	37	159	180	154	158	153	150	991
[No Tag]	24	153	148	142	143	122	105	837
Neurological	6	69	92	71	74	87	85	484
Cancer	21	123	109	102	111	115	113	694
Mortality	10	95	80	65	65	91	78	484
Gastrointestinal	9	62	66	64	68	65	64	398
Respiratory	12	68	55	47	56	70	53	361
Cardiovascular	5	44	35	34	36	29	34	217
Ocular and Sensory	4	55	47	44	44	47	54	295
Reproductive	8	23	26	33	30	31	35	186
Musculoskeletal	5	30	35	24	24	22	34	174
Renal	3	14	15	14	18	23	20	107
Skin and Connective Tissue	1	30	23	21	18	29	26	148
Total	**243**	**1,550**	**1,642**	**1,483**	**1,585**	**1,608**	**1,582**	**9,693**

Tag Browser Search Browse MeSH Tree Heatmap Browser Prioritized Lists

Document Preview Pie Chart Bar Chart

Health Outcomes

Evidence Stream

Tag	Code(s)	Count
[No Tag]		5171
Neurological		1097
Developmental		1066
Mortality		992
Hematological and Immune		816
Ocular and Sensory		75
Nutritional and Metabolic		720
Respiratory		628
Endocrine		597
Cardiovascular		558
Hepatic		381
Renal		379
Reproductive		379
Cancer		321
Gastrointestinal		305
Musculoskeletal		280
Skin and Connective Tissue		206

Tag	Code(s)	Count
[No Tag]		320
Human		518
Animal		384
In Vitro		158
Plant		67

1. Initial literature search; n = 9,537
2. Neurological; n = 1,097
3. Human; n = 518

Pulp and paper manufacture (Group 3)

Anonymous. *(1987)*

▼ Abstract

A. Evidence for carcinogenicity to humans (inadequate) Excess incidences of oral and pharyngeal and/or laryngeal cancers were reported in two studies designed to generate hypotheses. These cancer forms have not been evaluated in independent studies. Some studies, based on a few cases, suggest that an increased risk of lymphoproliferative neoplasms, particularly Hodgkin's disease, may be linked to employment in the pulp and paper industries. In a prospective cohort study of viscose workers exposed to carbon disulphide, 343 pulp and paper workers served as the reference group. During 15 years of follow-up, nine pulp and paper workers had died of lung cancer, compared with four viscose workers (rate ratio, 2.2; [95% confidence interval, 0.7-6.7]). The pulp and paper workers smoked slightly less than the viscose workers. When national rates were used as the reference, the SMR was 154 70-292). However, a US proportionate mortality study comprising 2113 deaths revealed no excess of lung cancer among pulp and paper workers. A US cohort study of 3572 pulp and paper mill workers employed for at least one year between 1945 and 1955 and followed until 1977 showed statistically nonsignificant excesses of lymphosarcoma and reticulosarcoma (10 cases; SMR, 169; 92-287) and of stomach cancer (17 cases; SMR, 123; 78-185). There was no excess of lung cancer. The excess of lymphosarcoma and reticulosarcoma was present only for men who had worked in sulphate mills (6 observed; SMR, 207; 90408), whereas the excess of stomach cancer occurred in sulphite mills (11 observed; SMR, 149; 83-246)5. Excesses of cancers at miscellaneous sites have been mentioned in some studies on pulp and paper workers. The finding may be due to chance, because the cases were generally few and the patterns inconsistent. A case-control study of the paternal

Showing 518 of 9537 loaded documents (1 selected; 0 total included; 0 total training docs.)

Score	Training Item?	Included?	RefID	Title	Year	Authors	Journal
0.243			h1994931	Pulp and paper manufacture (Group 3)	1987	Anonymous	
0.178			h1358122	Clinical and Experimental Studies of Distal Axonopathy -A Frequent Form of Brain and Nerve Damage Pr...	1979	Schaumburg, H. H.; Spencer, P. S.	
0.17			h654480	On the behaviour of the blood-brain barrier in carbon disulfide intoxication Original Title: Influenza della ...	1960	Bartonicek, V.; Michalova, C.	
0.153			h4226345	Unsafe behaviours at workplace and occupational exposure to organic solvents	2000	Bazylewicz-Walczak, B.	
0.151			h3062954	DDT and its derivatives	1979	IPCS,	
0.148			h1776126	Behavioral Toxicology	1983	Johnson, B. L.; Anger, W. K.	
0.146			h2971317	The Effects of Work Exposures on Organ Systems II Blood, Lungs and Nervous System	1981	Waldron, H. A.; Harrington, J. M.	
0.145			h1580225	Behavioral Teratology Of Industrial Solvents	1984	Nelson, B. K.	
0.144			h4225299	Human Behavioral Neurotoxicology; Workplace and Community Assessments	1992	Anger, W. K.; Johnson, B. L.	
0.143			h4057839	Neurologic and Behavioral Disorders	1988	Baker EL Jr	
0.142			h2210943	The Introduction and Monitoring of Occupational Diseases	1989	Baxter, P. J.; Waldron, H. A.	
0.141			h4224873	THE DOSE-RESPONSE RELATIONSHIPS IN NEUROPSYCHOLOGICAL STUDY OF CS-2 EXPOSED WORKERS	1997	Bazylewicz-Walczak, B.	
0.141			h23197	Chemicals affecting behavior	1985	Anger, W. K.; Johnson, B. L.; O'Donoghue, J. L.	
0.14			h2314443	PRINCIPLES AND METHODS FOR THE ASSESSMENT OF NEUROTOXICITY ASSOCIATED WITH EXPOSUR...	1986	WHO	
0.14			h1357939	Neurological Disorders	1983	Baker EL Jr	
0.105			h12292	Neurologic disease	1986	Rosenstock, L.; Cullen, M. R.	
0.104			h2072651	Neurobehavioural Effects	1995	Axelson, O.	
0.095			h4223998	Some mechanism of chronic carbon disulfide poisoning	1971	Telsinger, J.	
0.084			h1989587	NIOSH Report on Occupational Safety and Health for Fiscal Year 1983 Under Public Law 91-596	1984	Anonymous	
0.083			h4223903	The Action Of Carbon Disulfide Upon The Organism	1938	Lewy, F. H.	
0.077			h4223742	The Characterization And Diagnostic Significance Of Vestibular-Motor Disturbances In Patients With Chr...	1978	Nabiev, T. M.	
0.075			h4224881	Diseases Caused by Carbon Disulfide	1986	Anonymous	
0.07			h4223474	Carbon disulfide	1993	Anonymous	
0.07			h84553	Toxic effects of solvents and vapors	1991	Andrews, L. S.; Snyder, R.; Amdur, M. O.; Doull, J.; Klaassen, C. D.	

10:18 AM
5/15/2018

Targeting

SWIFT»REVIEW

Evidence Stream X Publication Year

	2017-2019	2015-2016	2013-2014
Aminal	31	261	310
Human	34	185	210
In vitro	18	105	137

⌘ **Distiller**SR

→ "Include" as key & tag

→ "Supplemental" & tag

→ "Exclude" & tag

Exposure Route X Publication Year

	2017-2019	2015-2016	2013-2014
Oral/Ingestion	31	261	310
Inhalation	34	185	210
Dermal	18	105	137

Based on TIAB does the article contain PECO relevant human or animal evidence?

○ Yes ○ No ● Supplemental material ○ unclear **Clear Response**

What kind of supplemental material?

☐ non-inhalation route

☐ MOA/mech (cancer)

☐ MOA/mech (non-cancer)

☑ in vitro

☐ ADME/toxicokinetic-related

☐ case report

☑ mixture/cigarette smoke

These data that can be tracked and visually displayed.

P	**Human:** Any population and life stage (e.g., children, general population, occupational or high exposure from an environmental source). The following study designs will be considered most informative: controlled exposure, cohort, case-control, cross-sectional and ecological. Note: Case reports and case series will be tracked during study screening, but are not the primary focus of this assessment. **Animal:** Nonhuman mammalian animal species (whole organism) of any life stage (including preconception, in utero, lactation, peripubertal, and adult stages).
E	**Human:** Exposure to acrolein via inhalation. Exposures quantified by either actual exposure measurements or occupational exposure history are preferred. Subchronic and chronic studies should be differentiated from shorter-term exposure durations. **Animal:** Any exposure to acrolein via inhalation. Studies involving exposures to mixtures will be included only if they include an arm with exposure to acrolein alone. Subchronic and chronic studies should be differentiated from shorter-term exposure durations. Toxicity studies using other routes of administration should be tagged during screening as supplemental material.
C	**Human:** A comparison or reference population exposed to lower levels (or no exposure/exposure below detection limits) of acrolein, or exposed to acrolein for shorter periods of time. **Animal:** A concurrent control group exposed to vehicle-only treatment.

SWIFT-Review Heatmap Generation

Export Tag Heatmap   ✕

Category 1 (Rows)   Health Outcomes

Category 2 (Columns)   Evidence Stream

Document Scope: All documents

Sheet Name: ChemA OutcomeXEvi Heatmap

Filepath for the results: Browse...

Ok   Cancel

Chemical B

	Animal	Human	In Vitro
Cancer	9	19	21
Cardiovascular	0	7	4
Developmental	2	12	30
Endocrine	2	3	4
Gastrointestinal	4	4	9
Hematological and Immune	6	21	21
Hepatic	6	2	6
Mortality	7	7	9
Musculoskeletal	1	3	2
Neurological	2	7	21
Nutritional and Metabolic	7	7	13
Ocular and Sensory	2	3	31
Renal	2	3	5
Reproductive	3	5	6
Respiratory	3	5	5
Skin and Connective Tissue	1	2	3
[No Tag]	1	26	155
Totals	58	136	345

SWIFT-Review Heatmap Generation

Export Tag Heatmap   ✕

Category 1 (Rows):   Health Outcomes

Category 2 (Columns):   Evidence Stream

Document Scope: All documents

Sheet Name: ChemA OutcomeXEvi Heatmap

Filepath for the results: Browse...

Ok   Cancel

Chemical B

	Animal	Human	In Vitro
Cancer	9	19	21
Cardiovascular	0	7	4
Developmental	2	12	30
Endocrine	2	3	4
Gastrointestinal	4	4	9
Hematological and Immune	6	21	21
Hepatic	6	2	6
Mortality	7	7	9
Musculoskeletal	1	3	2
Neurological	2	7	21
Nutritional and Metabolic	7	7	13
Ocular and Sensory	2	3	31
Renal	2	3	5
Reproductive	3	5	6
Respiratory	3	5	5
Skin and Connective Tissue	1	2	3
[No Tag]	1	26	155
Totals	58	136	345

Chemical C

	Animal	Human	In Vitro
Air Pollution	15	25	3

Air Pollution

(mesh_mh:("air pollution" OR "air pollutants" OR "particulate matter" OR smog OR soot OR "vehicle emissions" OR "motor vehicles")) OR pharm_actions:"air pollutants" OR (tiab: ("air pollution" OR "air pollutant" OR "air pollutants" OR "particulate matter" OR "PM2.5" OR "PM(2.5)" OR PM10 OR "PM(10)" OR smog OR soot OR "carbon black" OR "black carbon" OR "elemental carbon")) OR (tiab:((air OR airborne OR coarse OR ultrafine OR fine) AND (particle* OR particulate*))) OR (tiab:((vehicle OR vehicles OR vehicular OR auto OR automobile OR bus OR buses OR car OR truck* OR engine OR traffic OR transport*) AND (emissions OR exhaust OR fume*))) OR ((tiab:(air OR outdoor* OR outside OR ambient OR pollut* OR emissions OR exhaust*)) AND (((tiab:(S02 OR "sulfur dioxide" OR ozone OR O3 OR "hydrogen sulfide" OR H2S OR "carbon monoxide" OR "nitric oxide" OR "nitrogen oxide" OR "nitrogen oxides" OR "nitrogen dioxide" OR "NOx" OR "NO(x)" OR NO2))) OR (mesh_mh:("sulfur dioxide" OR ozone OR "hydrogen sulfide" OR "carbon monoxide" OR "nitrogen dioxide"))) OR mesh_mh:("volatile organic compounds" OR "fossil fuels") OR tiab:("volatile organic compounds" OR gasoline* OR diesel OR petrol*) OR mesh_mh_noexp:("Polycyclic hydrocarbons, aromatic") OR mesh_mh:("benzo(a)pyrene" OR benzene) OR tiab:("polycyclic aromatic hydrocarbon*" OR "benzopyrene" OR "benzo-a-pyrene" OR "3,4-benzopyrene" OR benzene)) OR tiab:(indoors OR "air quality") OR tiab:(indoor AND ("air pollution" OR smoke)) OR mesh_mh:("tobacco smoke pollution" OR smoking) OR tiab:("secondhand smoke" OR "secondhand smoking" OR "second hand smoke" OR "second hand smoking" OR "passive smoke" OR "passive smoking") OR tiab:((smoke OR smoking) AND (cigarette OR tobacco OR cigar*)) OR tiab:woodsmoke OR ((mesh_mh:wood OR tiab:(wood OR firewood OR biomass* OR charcoal OR fuel OR fuels OR gas OR gasoline OR kerosene OR dung OR manure)) AND (mesh_mh:smoke OR tiab:(smoke OR smoking OR combust* OR burn* OR burning))) OR mesh_mh:radon OR tiab:radon

Note:
- Not mutually exclusive
- Some references will likely be off-topic- screening still recommended!

Chemical C	Animal	Human	In Vitro
Air Pollution	15	25	3

Air Pollution

(mesh_mh:("air pollution" OR "air pollutants" OR "particulate matter" OR smog OR soot OR "vehicle emissions" OR "motor vehicles")) OR pharm_actions:"air pollutants" OR (tiab: ("air pollution" OR "air pollutant" OR "air pollutants" OR "particulate matter" OR "PM2.5" OR "PM(2.5)" OR PM10 OR "PM(10)" OR smog OR soot OR "carbon black" OR "black carbon" OR "elemental carbon")) OR (tiab:((air OR airborne OR coarse OR ultrafine OR fine) AND (particle* OR particulate*))) OR (tiab:((vehicle OR vehicles OR vehicular OR auto OR automobile OR bus OR buses OR car OR truck* OR engine OR traffic OR transport*) AND (emissions OR exhaust OR fume*))) OR ((tiab:(air OR outdoor* OR outside OR ambient OR pollut* OR emissions OR exhaust*)) AND (((tiab:(S02 OR "sulfur dioxide" OR ozone OR O3 OR "hydrogen sulfide" OR H2S OR "carbon monoxide" OR "nitric oxide" OR "nitrogen oxide" OR "nitrogen oxides" OR "nitrogen dioxide" OR "NOx" OR "NO(x)" OR NO2))) OR (mesh_mh:("sulfur dioxide" OR ozone OR "hydrogen sulfide" OR "carbon monoxide" OR "nitrogen dioxide")))) OR mesh_mh:("volatile organic compounds" OR "fossil fuels") OR tiab:("volatile organic compounds" OR gasoline* OR diesel OR petrol*) OR mesh_mh_noexp:("Polycyclic hydrocarbons, aromatic") OR mesh_mh:("benzo(a)pyrene" OR benzene) OR tiab:("polycyclic aromatic hydrocarbon*" OR "benzopyrene" OR "benzo-a-pyrene" OR "3,4-benzopyrene" OR benzene)) OR tiab:(indoors OR "air quality") OR tiab:(indoor AND ("air pollution" OR smoke)) OR mesh_mh:("tobacco smoke pollution" OR smoking) OR tiab:("secondhand smoke" OR "secondhand smoking" OR "second hand smoke" OR "second hand smoking" OR "passive smoke" OR "passive smoking") OR tiab:((smoke OR smoking) AND (cigarette OR tobacco OR cigar*)) OR tiab:woodsmoke OR ((mesh_mh:wood OR tiab:(wood OR firewood OR biomass* OR charcoal OR fuel OR fuels OR gas OR gasoline OR kerosene OR dung OR manure)) AND (mesh_mh:smoke OR tiab:(smoke OR smoking OR combust* OR burn* OR burning))) OR mesh_mh:radon OR tiab:radon

	Air Pollution	Allergens	Diet and Nutrition	Drugs of Abuse	Endocrine Disruptors	Flame Retardants	General Environmental Exposures	Heavy Metals	Ionizing Radiation	Miscellaneous	Occupational	Pesticides	Phthalates	Polycyclic Aromatic Hydrocarbons	Solvents	Stress
Cancer	51	11	117	109	2	0	213	164	117	13	20	17	1	21	5	53
Cardiovascular	46	25	147	204	1	0	129	143	23	19	7	21	2	4	10	137
Developmental	75	36	406	236	6	2	265	431	99	25	28	55	4	12	26	174
Endocrine	71	19	667	528	17	2	685	1078	89	92	28	214	11	52	77	201
Gastrointestinal	26	26	263	160	0	0	138	165	34	14	12	26	2	9	13	44
Hematological and Immune	124	163	465	197	2	0	414	551	120	42	56	83	11	16	44	142
Hepatic	12	3	193	157	2	0	143	191	28	16	10	56	4	19	15	43
Mortality	36	14	134	99	2	2	118	263	65	13	23	43	1	4	8	60
Musculoskeletal	19	14	119	162	1	0	140	197	54	18	18	39	1	6	12	74
Neurological	40	17	180	409	3	1	199	312	23	25	31	47	4	10	20	267
Nutritional and Metabolic	40	14	678	243	4	1	244	371	29	37	11	99	10	23	31	138
Ocular and Sensory	37	116	62	113	0	0	152	141	31	14	9	19	0	6	16	74
Renal	22	11	110	82	1	0	105	115	12	11	15	19	1	9	15	24
Reproductive	22	8	181	126	9	2	99	151	46	6	6	22	2	8	10	71
Respiratory	114	69	53	149	2	1	108	106	32	13	27	36	3	12	11	85
Skin and Connective Tissue	20	65	85	51	2	0	77	76	27	9	5	18	1	4	6	24

General Environmental Exposures

(mesh_mh:("specialty uses of chemicals" OR "toxic actions")) OR

(mesh_mh_noexp:(environment OR "environmental pollutants" OR "noxae" OR "environmental pollution")) OR

(mesh_mh:("air pollutants" OR "carcinogens, environmental" OR "endocrine disruptors" OR "hazardous substances" OR "water pollutants" OR "carcinogens" OR "cardiotoxins" OR "cytotoxins" OR "dermotoxins" OR "immunotoxins" OR "mutagens" OR "neurotoxins" OR "teratogens" OR "pesticides" OR "air pollution" OR "environmental exposure" OR "water pollution")) OR

(pharm_actions:("hazardous substances" OR "environmental pollutants")) OR

(tiab:(xenobiotic* OR xenoestrogen*)) OR

(tiab:("environmental agent*" OR "environmental chemical*" OR "environmental compound*" OR "environmental contaminant*" OR "environmental determinant*" OR "environmental estrogen*" OR "environmental exposure*" OR "environmental factor*" OR "environmental influence*" OR "environmental stress*" OR "environmental epigenetic*")) OR

(tiab:(carcinogen OR carcinogens OR carcinogenic OR teratogen OR teratogenic OR mutagen OR mutagens OR mutagenic OR pollutant* OR pollution OR cardiotox* OR dermotox* OR immunotox* OR nephrotox* OR neurotox* OR toxicant* OR toxin*))

OR (mesh_mh:teratogens) OR (title:(environment* AND epigen*)) OR

(tiab:("chemical compound*" OR "chemical exposure*" OR "chemical mixture*" OR "chemical product*" OR "chemical substance*" OR "hazardous compound*" OR "hazardous exposure*" OR "hazardous mixture*" OR "hazardous product*" OR "hazardous substance*" OR "industrial compound*" OR "industrial chemical*"))

Potential New SWIFT Exposure Template

	Sources, Production, Uses	Environmental Fate & Transport	Environmental Media	Environmental Concentrations	Exposure Route	Human Exposure Estimate and Dose	Human Biomonitoring Data	Special Populations Groups of Concern	Exposure Setting (Indoor, Outdoor, etc.)	Occupational	Consumer Products
Chemical A	1	0	1	6	10	0	0	0	0	0	0
Chemical B	0	0	2	0	0	2	0	2	0	3	0
Chemical C	1	0	1	0	0	0	0	0	0	0	0
Chemical D	0	4	1	0	1	0	0	1	0	0	0
Chemical E	2	0	3	0	1	1	1	0	0	0	0
Chemical F	0	0	2	1	2	0	0	0	4	0	0
Chemical G	4	0	1	0	0	2	0	0	0	1	0
Chemical H	0	0	0	1	2	0	0	0	0	0	1
Totals	8	4	11	8	16	5	1	3	4	4	1

General Exposure> Environmental Media > Media Specific

Export Tag Heatmap ✕

Category 1 (Rows): **General Exposure**

Category 2 (Columns): **Chemical** v

Document Scope: All documents

Sheet Name: GenExpXChem Heatmap

Filepath for the results: [   ] Browse...

Ok   Cancel

	Sources, Production, Uses	Environmental Fate & Transport	Environmental Media	Environmental Concentrations	Exposure Route	Human Exposure Estimate and Dose	Human Biomonitoring Data	Special Populations Groups of Concern	Exposure Setting (Indoor, Outdoor, etc.)	Occupational	Consumer Products
Chemical A	1	0	1	6	10	0	0	0	0	0	0
Chemical B	0	0	2	0	0	2	0	2	0	3	0
Chemical C	1	0	1	0	0	0	0	0	0	0	0
Chemical D	0	4	1	0	1	0	0	1	0	0	0
Chemical E	2	0	3	0	1	1	1	0	0	0	0
Chemical F	0	0	2	1	2	0	0	0	4	0	0
Chemical G	4	0	1	0	0	2	0	0	0	1	0
Chemical H	0	0	0	1	2	0	0	0	0	0	1
Totals	8	4	11	8	16	5	1	3	4	4	1

Granularity:

General Exposure> Environmental Media > Media Specific

Granularity:

General Exposure> Environmental Media > Media Specific

Export Tag Heatmap ✕

Category 1 (Rows)	**Exposure Media** ⌄
Category 2 (Columns)	**Chemical** ⌄
Document Scope:	All documents ⌄
Sheet Name:	GenExpXChem Heatmap
Filepath for the results:	

Ok Cancel

	Environmental Media	Air Total	Air - Indoors	Air - Outdoors	Water	Soil	Dust	Biomonitoring	Fish	Food	Drinking Water
Chemical A	4	0	1	6	0	0	0	0	0	0	10
Chemical B	4	0	2	0	2	0	2	0	3	0	2
Chemical C	1	0	1	0	0	0	0	0	0	0	0
Chemical D	6	4	1	0	0	0	1	0	0	0	1
Chemical E	5	0	3	0	1	1	0	0	0	0	1
Chemical F	7	0	2	1	0	0	0	4	0	0	2
Chemical G	4	0	1	0	2	0	0	0	1	0	0
Chemical H	4	0	0	1	0	0	0	0	0	1	2
Totals	7	4	11	8	5	1	3	4	4	1	18

Granularity:

General Exposure> **Environmental Media >** Media Specific

Export Tag Heatmap ✕

Category 1 (Rows)	Exposure Media ⌄	
Category 2 (Columns)	Chemical ⌄	
Document Scope:	All documents ⌄	
Sheet Name:	GenExpXChem Heatmap	
Filepath for the results:		

Ok   Cancel

	Environmental Media	Air Total	Air - Indoors	Air - Outdoors	Water	Soil	Dust	Biomonitoring	Fish	Food	Drinking Water
Chemical A	4	0	1	6	0	0	0	0	0	0	10
Chemical B	4	0	2	0	2	0	2	0	3	0	2
Chemical C	1	0	1	0	0	0	0	0	0	0	0
Chemical D	6	4	1	0	0	0	1	0	0	0	1
Chemical E	5	0	3	0	1	1	0	0	0	0	1
Chemical F	7	0	2	1	0	0	0	4	0	0	2
Chemical G	4	0	1	0	2	0	0	0	1	0	0
Chemical H	4	0	0	1	0	0	0	0	0	1	2
Totals	7	4	11	8	5	1	3	4	4	1	18

Granularity:

General Exposure> Environmental Media > **Media Specific**

Export Tag Heatmap   ✕

Category 1 (Rows) | **Water Specific Categories** ∨

Category 2 (Columns) | **Chemicals** ∨

Document Scope: All documents

Sheet Name: **Water**

Filepath for the results:

Ok

	Water	Aquifer	Dam*	Hydrolog*	Groundwater	River	Lake	Stream	Reservoir	Irrigation	Effluent
Chemical A	40	0	1	6	0	0	0	0	0	0	10
Chemical B	4	0	2	0	2	0	2	0	3	0	2
Chemical C	1	0	1	0	0	0	0	0	0	0	0
Chemical D	6	4	1	0	0	0	1	0	0	0	1
Chemical E	5	0	3	0	1	1	0	0	0	0	1
Chemical F	7	0	2	1	0	0	0	4	0	0	2
Chemical G	4	0	1	0	2	0	0	0	1	0	0
Chemical H	4	0	0	1	0	0	0	0	0	1	2
Totals	71	4	11	8	5	1	3	4	4	1	18
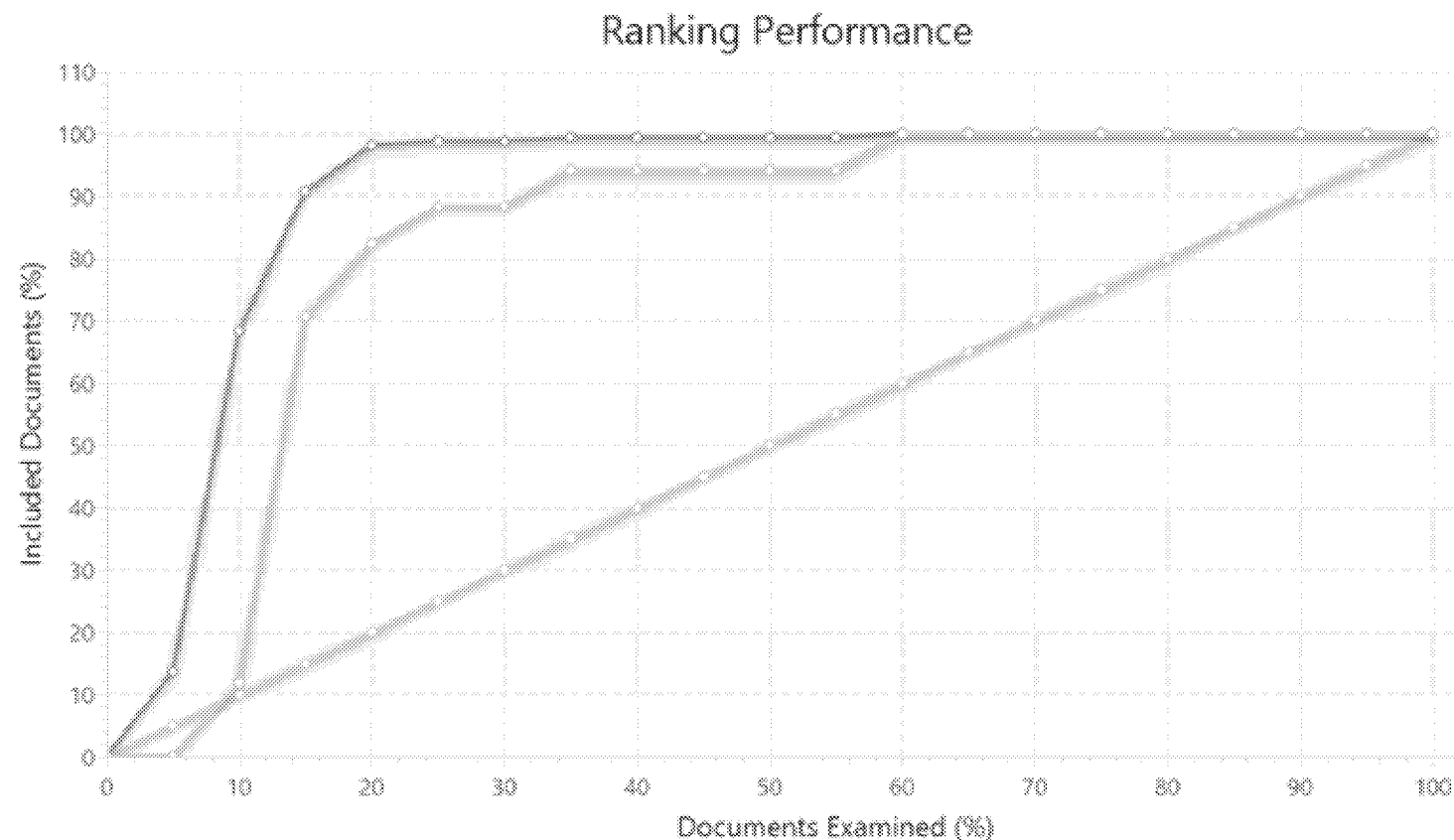
Ranking Performance

Included Documents (%) — y-axis (0 to 110)
Documents Examined (%) — x-axis (0 to 100)

Randomized Documents   Ranked Documents (All)   Ranked Documents (Test)

Use a set of known references (aka "seeds") to help train SWIFT-Review to identify relevant references.

Score	Training Item?	Included?	RefID	Title	Year
0.757	☑	☑	28064477	Fast Optimization of LiMgMnOx/La2O3 ...	2017
0.724	☐	☐	28193168	Genome-wide SNP identification, linkag...	2017
0.715	☑	☑	28046029	Genetic Variants in MTHFR Gene Predic...	2017
0.697	☑	☑	27697424	Green and facile method for the recove...	2017
0.586	☑	☐	26061418	Genome-wide association mapping of c...	2015
0.58	☑	☐	26627913	Conversion Reaction-Based Oxide Nano...	2016
0.573	☑	☑	27507976	Natural Genetic Variation of Seed Micro...	2016
0.569	☐	☐	3696229	Genome mapping.	1987

'Included' documents are highlighted in yellow and 'excluded' are circled in red

Showing 13,642 of 49,911 documents (171 included; 1,532 total training docs)

Developing chemical-free "organic" seed that can be used to target exposure studies regardless of the chemical.

Slide provided by M. Angrish; modified by A. Wilkins

Acknowledgements

Exposure & Fate Search String & Tagging Development Experts and Oversight Team

- Steven Dutton
- Emma Lavoie
- Janice Lee
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- John Wambaugh

IRIS Manual Tagging Team

- Carolyn Gigot
- Andrew Greenhalgh
- Kelly Garcia
- Michele Taylor
- Michelle Angrish
- Amina Wilkins

SR Data Visualization

- Screener data – names, number, amount of time spent reviewing, etc.
- References and bibliographic information
- 'Included' and 'Excluded' references (including counts for each)
- Tags (Included, Supplemental, Excluded)

Visualizing Data

Distiller screener data output

User Metrics

Date	User	First Submission	Last Submission	Difference	References Submitted	Average Time Per Reference	Median of Time Per Reference	Time Spent Reviewing
11-20-2017	First.Reviewer@epa.gov	0.65	0.69375	1h 3m 12s	65	1m 23s	40s	1h 29m 55s
11-21-2017	No Submissions for this date							
11-22-2017	No Submissions for this date							

Screening Form Completion Time
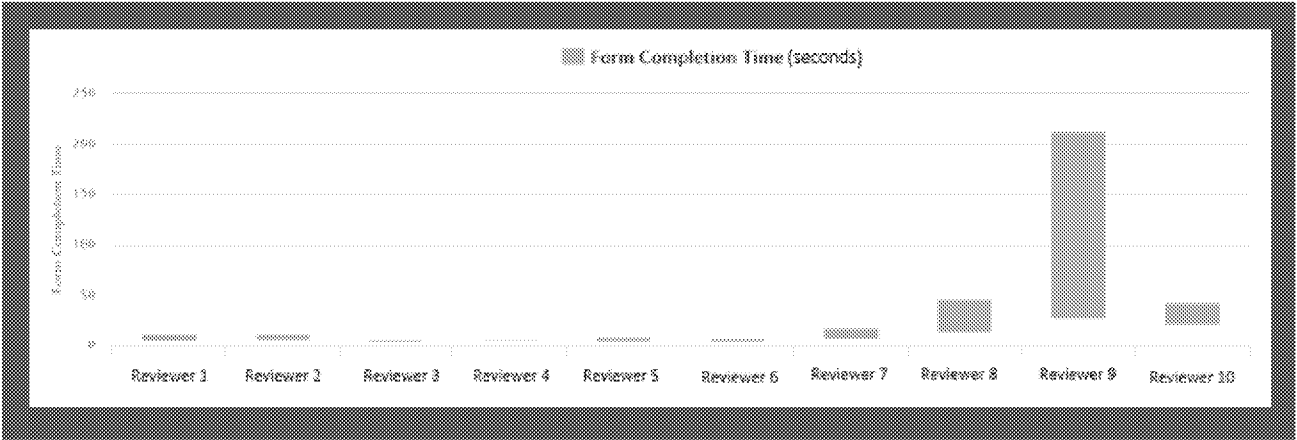
User Workload

Flow Chart Visual

Database Searches (1992 to October 2018)

| PubMed (520) | WOS (1,102) | ToxLine (1,600) | ChemView (n =) | OPP 2018 (n =) | Other (n = 0) |

TITLE AND ABSTRACT

Title & Abstract (TIAB) Screening
(2827 records after duplicate removal*)

→ **Excluded (n= 2457)**
- Not relevant to PECO or tagged as supplemental material (n = 1,205)
- Unresolved conflicts (n-186)
- Tagged as supplemental material by at least one reviewer (n = 1,066)

FULL TEXT

Full-Text Screening
(total n = 185)

Published During or After 2005
(n = 25)

→ **Excluded (n= 12)**
- Not relevant to PECO or tagged as supplemental material (n = 0)
- Tagged as supplemental material (n = 12)

Studies Characterized in Health Inventory (n = 13)
- *Human health effects studies (n = 7)*
  - cancer (1) metabolic (1)
  - endocrine (1) neurological (1)
  - hematologic (1) renal (1)
  - hepatic (1) respiratory (2)

- *Animal health effect studies (n =6)*
  - developmental (3) immune (2)
  - endocrine (2) renal (2)
  - hepatic (2) reproductive (3)
  - systemic (1)

Tagged as supplemental at either TIAB or full-text level (n= 1078)
- Mechanistic, cancer (n = 172)
- Mechanistic, non-cancer/unclear (n = 128)
- Non-mammalian model (n = 59)
- ADME/toxicokinetic (n = 94)
- Exposure characterization (n = 248)
- Susceptible population (n = 12)
- Case report/case series (n = 41)
- Non-PECO route of exposure (n = 2)
- Records with no original data (e.g., reviews, assessments, editorials, commentaries) (n = 218)
- Conference abstract (n = 15)
- Mixture study (n = 52)

*2,828 records were provided by HERO after removing duplicates but another duplicate was fund during full-text review and was quarantined in DistillerSR, bringing the total to 2,827.

Visualization Software
- Distiller, PRISMA template

Results are coordinated with HERO

Interactive Tables

Figure 7. Summary of main findings in new epidemiological studies
Click here to view the interactive version and a more detailed description of findings and exposure assessment.

Reference	Population	Health System	Study Design	Chemical	Results	Exposure Assessment			
						air	blood, serum, or plasma	occupational	urine
Heck et al, 2013	children	Cancer	case-control	1,4 dichlorobenzene	positive association	▣			
Kalkbrenner et al, 2018	children	Nervous	case-control	1,4 dichlorobenzene	negative association	▣			
Elliott et al, 2006	general population	Respiratory	cross-sectional	1,4 dichlorobenzene	positive association		▣		
Buckley et al, 2018	children	Respiratory	cross-sectional	metabolite: 2,5-dichlorophenol (2,5-DCP)	positive association				▣
Wei and Zhu, 2016a	general population	Metabolic	cross-sectional	metabolite: 2,5-dichlorophenol (2,5-DCP)	positive association				▣
Wei and Zhu, 2016b	children	Endocrine	cross-sectional	metabolite: 2,5-dichlorophenol (2,5-DCP)	positive association				▣
Hsiao et al, 2009	occupational	Hematologic	cross-sectional	metabolite: 2,5-dichlorophenol (2,5-DCP)	positive association			▣	
		Hepatic	cross-sectional	metabolite: 2,5-dichlorophenol (2,5-DCP)	positive association			▣	
		Renal	cross-sectional	metabolite: 2,5-dichlorophenol (2,5-DCP)	positive association			▣	

Interactive Data Tables

Document

Interactive Data Tables

Document

Favorite   Download

Reference	Population	Health System	case-control	cohort	cross-sectional
Kim et al, 2016	infants	endocrine	▦		
Dong et al., 2013	children	respiratory	▦		
Lee et al., 2018	children	developmental			▦
Smit et al, 2015	children	immune			▦
Callan et al., 2016	pregnant women	developmental			▦
Hoyer et al., 2017	pregnant women	nervous		▦	
Monroy et al., 2008	pregnant women	developmental			▦
Rahman et al., 2019	pregnant women	endocrine		▦	
Bloom et al, 2010	general population	endocrine			▦
Fu et al, 2014	general population	cardiovascular			▦
Huang et al., 2018	general population	cardiovascular			▦
Kielsen et al., 2017	general population	immune		▦	
Lind et al, 2014	general population	endocrine			▦
Wang et al., 2017	general population	reproductive	▦		
Mattsson et al., 2015	occupational	cardiovascular		▦	

Evidence Type
- [ ] (All)
- [ ] Animal
- [x] Human

Results
- ▦ association with pote…
- ▦ insufficient samples >…
- ▦ inverse associaiton wi…
- ▦ no association

adverse health effects

Reference	Population	Health System	case-control	cohort	cross-sectional
Kim et al, 2016	infants	endocrine	▦		
Dong et al., 2013	children	respiratory		▦	
Lee et al., 2018	children	developmental			
Smit et al, 2015	children	immune			
Callan et al., 2016	pregnant women	developmental			▦
Hoyer et al., 2017	pregnant women	nervous			▦
Monroy et al., 2008	pregnant women	developmental			▦
Rahman et al., 2019	pregnant women	endocrine		▦	
Bloom et al 2010	general population	endocrine			
Fu et al, 2014	general population	cardiovascular			
Huang et al., 2018	general population	cardiovascular			
Kielsen et al., 2017	general population	immune			
Lind et al, 2014	general population	endocrine			
Wang et al., 2017	general population	reproductive	▦		
Mattsson et al., 2015	occupational	cardiovascular		▦	

Interactive Data Tables

- Hover to get additional info
- Experimenting with different data visualization tools

Qlik Sense

Evidence Stream X Outcome Example

	Animal (m.	Human	In vitro
acute Toxicity/Poiso..	9	1	
ADME/toxicokinetic	5	6	
apoptosis			1
Apoptosis, Cytotoxic..			1
asthma and rhinitis		1	
body weight	9		
cancer	1	1	
cardiovascular	26	3	
clinical chemistry/b..	6		
gene expression/omic..	16	1	3
growth (early life) ..	1		
hematological	2		
hepatic	1		1
hyperplasia and squa..	5		
immune/inflammation	29	3	2
lipid peroxidation	1		
neurological/behavio..	9	7	
nutrition and metabo..	1		

PECO-relevant 🔍   Bibliography 🔍   🔍

		1
⊕ No		26
⊕ Supplemental material		55
⊕ Unclear		11
⊕ Yes		57
⊕ Yes, but not likely useful for toxicity value purposes		

Level 🔍	PECO-relevant 🔍	Bibliography 🔍
1	No	1313602 A. J. De Vos, F. Reisen, A. Cook, B. Devine, P. Weinstein. 2009. Respiratory irritants in Australian bushfire smoke: air toxics sampling in a smoke chamber and during prescribed burns. Archives of Environmental
1	No	1313698 A. J. De Vos, A. Cook, B. Devine, P. J. Thompson, P. Weinstein. 2006. Effect of protective filters on fire fighter respiratory health during simulated bushfire smoke exposure. American Journal of Industrial
1	No	1319827 E. Roemer, M. K. Schorp, J. J. Piade, J. I. Seeman, D. E. Leyden, H. J. Haussmann. 2012. Scientific assessment of the use of sugars as cigarette tobacco ingredients: A review of published and other publicly
1	No	1331842 E. Eckert, K. Schmid, B. Schaller, K. Hiddemann-Koca, H. Drexler, T. Göen. 2011. Mercapturic acids as metabolites of alkylating substances in urine samples of German inhabitants. International Journal of Hygiene
1	No	1455636 S. G. Carmella, M. Chen, S. Han, A. Briggs, J. Jensen, D. K. Hatsukami, S. S. Hecht. 2009. Effects of smoking cessation on eight urinary tobacco carcinogen and toxicant biomarkers. Chemical Research
1	No	1787997 P. Jacob, A. H. Abu Raddaha, D. Dempsey, C. Havel, M. Peng, L. Yu, N. L. Benowitz. 2013. Comparison of nicotine and carcinogen

Qlik Sense

Evidence Stream X Outcome Example

	Animal (m...	Human	In vitro
acute Toxicity/Poiso...	9	1	
ADME/toxicokinetic	5	5	
apoptosis			1
Apoptosis, Cytotoxic...			1
asthma and rhinitis		1	
body weight	9		
cancer	1	1	
cardiovascular	26	3	
clinical chemistry/b...	8		
gene expression/omic...	16	1	3
growth (early life) ..	1		
hematological	2		
hepatic	1		1
hyperplasia and squa...	5		
immune/inflammation	29	3	2
lipid peroxidation	1		
neurological/behavio...	9	7	
nutrition and metabo...	1		

PECO-relevant 🔍	Bibliography 🔍		🔍
			1
⊕ No			26
⊕ Supplemental material			55
⊕ Unclear			11
⊕ Yes			57
⊕ Yes, but not likely useful for toxicity value purposes			

Level 🔍	PECO-relevant 🔍	Bibliography 🔍
1	No	1313602 A. J. De Vos, F. Reisen, A. Cook, B. Devine, P. Weinstein. 2009. Respiratory irritants in Australian bushfire smoke: air toxics sampling in a smoke chamber and during prescribed burns. Archives of Environmental
1	No	1313698 A. J. De Vos, A. Cook, B. Devine, P. J. Thompson, P. Weinstein. 2006. Effect of protective filters on fire fighter respiratory health during simulated bushfire smoke exposure. American Journal of Industrial
1	No	1319827 E. Roemer, M. K. Schorp, J. J. Piade, J. I. Seeman, D. E. Leyden, H. J. Haussmann. 2012. Scientific assessment of the use of sugars as cigarette tobacco ingredients: A review of published and other publicly
1	No	1331842 E. Eckert, K. Schmid, B. Schaller, K. Hiddemann-Koca, H. Drexler, T. Göen. 2011. Mercapturic acids as metabolites of alkylating substances in urine samples of German inhabitants. International Journal of Hygiene
1	No	1455636 S. G. Carmella, M. Chen, S. Han, A. Briggs, J. Jensen, D. K. Hatsukami, S. S. Hecht. 2009. Effects of smoking cessation on eight urinary tobacco carcinogen and toxicant biomarkers. Chemical Research
1	No	1787997 P. Jacob, A. H. Abu Raddaha, D. Dempsey, C. Havel, M. Peng, L. Yu, N. L. Benowitz. 2013. Comparison of nicotine and carcinogen

ED_004465_00012138-00060

Qlik Sense

Evidence Stream X Outcome Example

cardiovascular **3** Human

PECO-relevant 🔍	Bibliography 🔍		Level 🔍	
			1	2
⊙ Supplemental material			1	~
⊙ Yes			1	~
⊙ **Yes, but not likely useful for toxicity value purposes**			~	1

Level 🔍	PECO-relevant 🔍	Bibliography 🔍
1	Supplemental material	4096547 G. Thiriez, M. Bouhaddi, L. Mourot, F. Nobili, J. O. Fortrat, A. Menget, P. Franco, J. Regnard. 2009. Heart rate variability in preterm infants and maternal smoking during pregnancy. Clinical Autonomic
1	Yes	4088940 M. Yoshida, T. Mikami, K. Higashi, R. Saiki, M. Mizoi, K. Fukuda, T. Nakamura, I. Ishii, K. Nishimura, T. Toida, H. Tomitori, K. Kashiwagi, K. Igarashi. 2012. Inverse correlation between stroke and urinary
2	Yes, but not likely useful for toxicity value purposes	4088531 N. Dejarnett, D. J. Conklin, D. W. Riggs, J. A. Myers, T. E. O'Toole, I. Hamzeh, S. Wagner, A. Chugh, K. S. Ramos, S. Srivastava, D. Higdon, D. J. Tollerud, A. Defilippis, C. Becher, B. Wyatt, J. Mccracken, W. Abplanalp,

Qlik Sense

Evidence Stream X Outcome Example

	Animal (mu	Human	In vitro
gene expression/omic...	16	1	3

	Animal (mu	Human	In vitro
acute Toxicity/Poiso...	9	1	
ADME/toxicokinetic	6	5	
apoptosis			1
Apoptosis, Cytotoxic...			1
asthma and rhinitis		1	
body weight	5		
cancer	1	1	
cardiovascular	26	3	
clinical chemistry/b...	5		
gene expression/omic...	16	1	3
growth (early life) ...	1		
hematological	2		
hepatic	1		1
hyperplasia and squa...	9		
immune/inflammation	29	3	2
lipid peroxidation			1
neurological/behavio...	9	5	
nutrition and metabo...		1	

PECO-relevant 🔍	Bibliography 🔍		Level 🔍	
			1	2
⊕ Supplemental material			6	-
⊕ Yes			8	3
⊕ Yes, but not likely useful for toxicity value purposes			-	3

Level 🔍	PECO-relevant 🔍	Bibliography 🔍
1	Supplemental material	2976280 D. J. Conklin, R. A. Prough, P. Juvan, T. Rezen, D. Rozman, P. Haberzettl, S. Srivastava, A. Bhatnagar. 2011. Acrolein-induced dyslipidemia and acute-phase response are independent of HMG-CoA
1	Supplemental material	4088072 W. Y. Chen, M. Wang, J. Zhang, S. S. Barve, C. J. Mcclain, S. Joshi-Barve. 2017. Acrolein Disrupts Tight Junction Proteins and Causes Endoplasmic Reticulum Stress-Mediated Epithelial Cell Death Leading to
1	Supplemental material	4088083 R. Takamiya, K. Uchida, T. Shibata, T. Maeno, M. Kato, Y. Yamaguchi, S. Ariki, Y. Hasegawa, A. Saito, S. Miwa, H. Takahashi, T. Akaike, Y. Kuroki, M. Takahashi. 2017. Disruption of the structural and
1	Supplemental material	4088277 K. L. Wang, W. C. Huang, J. C. Chou, T. C. Weng, S. Hu, F. K. Lieu, W. H. Lai, G. Idova, P. S. Wang, S. W. Wang. 2016. Effects of acrolein on aldosterone release from zona glomerulosa cells in male rats. Steroids.
1	Supplemental material	4088328 M. J. Randall, G. R. Haenen, F. G. Bouwman, A. van der Vliet, A. Bast. 2016. The tobacco smoke component acrolein induces glucocorticoid resistant gene expression via inhibition of histone
1	Supplemental material	4089642 A. Tanel, D. A. Averill-Bates. 2007. Activation of the death receptor pathway of apoptosis by the aldehyde acrolein. Free Radical

Qlik Sense - Supplemental

Evidence Stream X Outcome Example

	Animal (mu	Human	In vitro
ADME/toxicokinetic	1	2	
apoptosis			1
Apoptosis, Cytotoxic...			1
cardiovascular	1	1	
gene expression/omic...	4		6
hepatic	1		1
immune/inflammation	1		7
lipid peroxidation	1		
neurological/behavio...	5	1	
other	4		4
oxidative stress	5		
protein carbonylatio...			1
renal/urinary	1		
respiratory	4	4	1
sensory	1		
sensory irritation	1		
signal transduction			1

PECO-relevant	Bibliography		Level	1	2
No				26	4
Supplemental material				55	15
Unclear				11	-
Yes				57	168
Yes, but not likely useful for toxicity value purposes				-	23

Level	PECO-relevant	Bibliography
1	Supplemental material	1062699 S. S. Hecht, A. Seow, M. Wang, R. Wang, L. Meng, W. P. Koh, S. G. Carmella, M. Chen, S. Han, M. C. Yu, J. M. Yuan. 2010. Elevated levels of volatile organic carcinogen and toxicant biomarkers in Chinese women
1	Supplemental material	1073890 D. N. Willis, B. Liu, M. A. Ha, S. E. Jordt, J. B. Morris. 2011. Menthol attenuates respiratory irritation responses to multiple cigarette smoke irritants. FASEB Journal. 2011. 25:4434-4444
1	Supplemental material	1074357 C. J. Shepperd, A. C. Eldridge, G. Errington, M. Dixon. 2011. A study to evaluate the effect on Mouth Level Exposure and biomarkers of exposure estimates of cigarette smoke exposure following a forced switch
1	Supplemental material	1076648 H. M. Lee, L. M. Hallberg, G. H. Greeley, E. W. Englander. 2010. Differential inhibition of mitochondrial respiratory complexes by inhalation of combustion smoke and carbon monoxide, in vivo, in the rat brain.
1	Supplemental material	1641966 V. T. Rummenie, Y. Matsumoto, M. Dogru, Y. Wang, Y. Hu, S. K. Ward, A. Igarashi, T. Wakamatsu, O. Ibrahim, E. Goto, G. Luyten, H. Inoue, I. Saito, J. Shimazaki, K. Tsubota. 2008. Tear cytokine and ocular surface
1	Supplemental material	2223954 H. S. Deshmukh, A. Mclachlan, J. J. Atkinson, W. D. Hardie, T. R. Korfhagen, M. Dietsch, Y. Liu, P. Y. P. Di, S. C. Wesselkamper, M. T.

Recap & Next Steps

- Develop the exposure and fate search strings
- QA the search strings using SWIFT-Review
- Develop the "organic" chemical-free seeds for SWIFT-Review
- Make the search strings and seeds available to the public
- Further refine our interactive visuals

Thank you!

- Kris Thayer
- Janice Lee
- Toxic Pathways Branch
- Manual Tagging Team
- Exposure & Fate Literature Search String Development Experts

Summary & Questions

- Develop the exposure and fate search strings
- QA the search strings using SWIFT-Review
- Develop the "organic" chemical-free seeds for SWIFT-Review
- Make the search strings and seeds available to the public
- Further refine our interactive visuals

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IRIS Program

Wilkins.Amina@epa.gov
(202) 564-1224

Active Links

- Color coded severity by study design

- Exposure assessment parameters

- Qlik example

Active Links

- [Color coded severity by study design](#)

- [Exposure assessment parameters](#)

- [https://public.tableau.com/profile/kris.chialton#!/vizhome/14Dichloroben zene1-13-2019/HumanFindings?publish=yes](#)

- [Qlik example](#)

- [https://qlikviz.epa.gov/sense/app/70a09bec-5c6f-494c-bd70- dd33b2138547/sheet/c50c2930-9f01-47de-b37a- bd19499b6493/state/analysis?qlikTicket=0I2P7vl0GNZO87ut](#)

2. Use ranking performance (blue line) and test set (green line) score to prioritize studies for screening
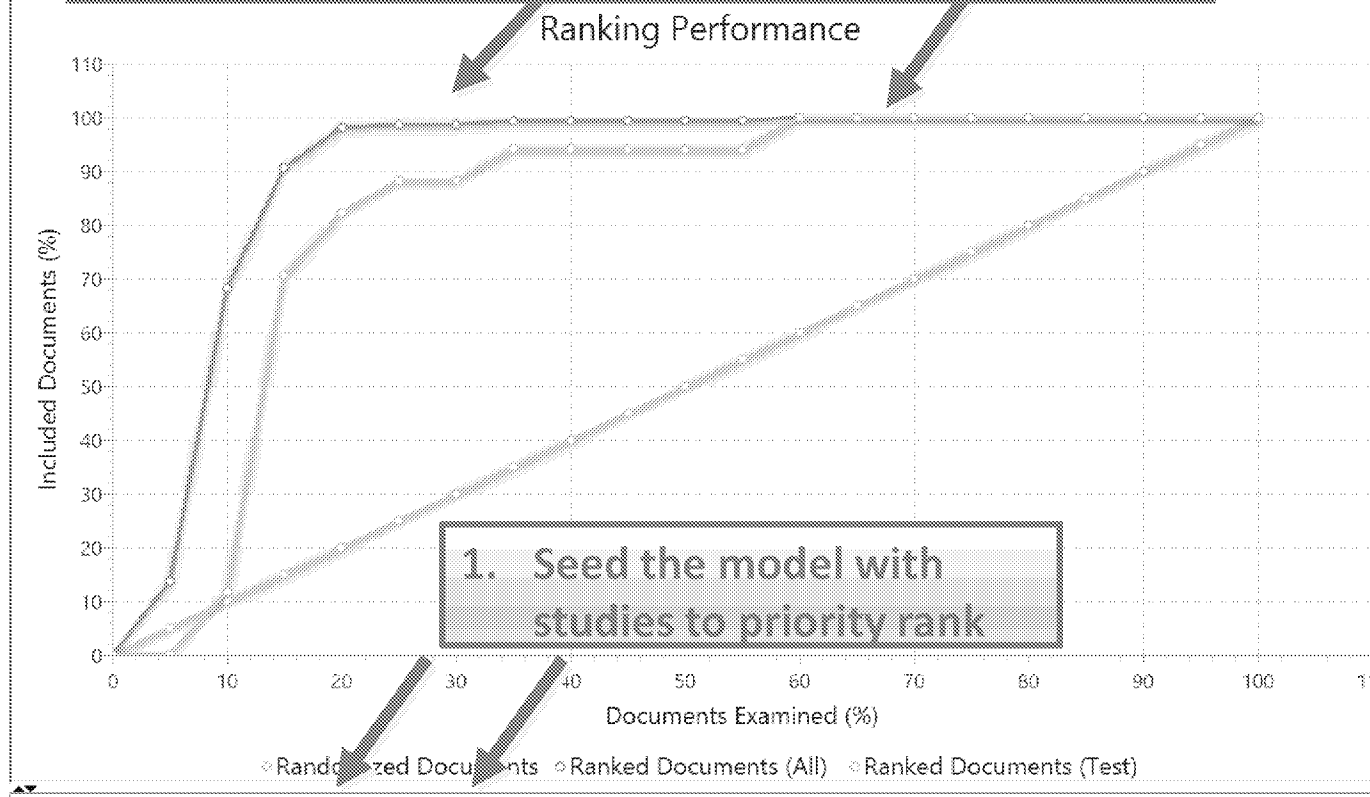
Use a set of known references (aka "seeds") to help train SWIFT-Review to identify relevant references

Ranking Performance

Developmental toxicity studies of triethylene glycol monomethyl ether ac rabbits

Hoberman, A. M.; Krasavage, W. J.; Christian, M. S.; Stack, C. R. *Journal of the American College of Toxicology* (1996)

▼ Abstract

Triethylene glycol monomethyl ether (TGME) was administered orally via gavage stomach tube to mated Caesarean delivered (CD) rats and artificially i gestation, respectively, at dose levels of 0, 625, 1,250, 2,500, or 5,000 mg/kg/day (rats) and 0, 250, 500, 1,000, or 1,500 mg/kg/day (rabbits). Clinica monitored throughout the treatment period. The surviving rats and rabbits underwent Caesarean section on day 20 and day 29 of gestation, respectively tissue and skeletal alterations. In rats, the high dose significantly reduced maternal body weights, feed consumption, and gravid uterine weights. One dam

Y-axis: Included Documents (%)
X-axis: Documents Examined (%)

Score	Training Item?	Included?	RefID	Title	Year
0.757	☑	☑	28064477	Fast Optimization of LiMgMnOx/La2O3 ...	2017
0.724	☐	☐	28193168	Genome-wide SNP identification, linkag...	2017
0.715	☑	☑	28046...	Genetic Variants in MTHFR Gene Predict...	2017
0.697	☑	☑	27697424	Green and facile method for the recove...	2017
0.586	☑	☐	26061418	Genome-wide association mapping of c...	2015
0.58	☑	☐	26627913	Conversion Reaction-Based Oxide Nano...	2016
0.573	☑	☑	27507976	Natural Genetic Variation of Seed Micro...	2016
0.569	☐	☐	3696229	Genome mapping.	1987

'Included' documents are highlighted in yellow and 'excluded' are circled in red

1. Seed the model with studies to priority rank

◇ Randomized Documents ○ Ranked Documents (All) ◇ Ranked Documents (Test)

Showing 13642 of 49911 loaded documents (1 selected; 171 total included; 1532 total training docs.)

Score	Training Item?	Included?	RefID	Title	Year	Authors	Journal
0.657		✓	s8	Potential reversibility of skeletal effects in rats exposed in utero to caffeine	1987	Collins, T. F.; Welsh, J. J.; Black, T. N.; Whitby, K. E.; O'Donnell, M. W.	Food Chem Toxicol
0.71		✓	s6	Significance of 2-methoxypropionic acid formed from beta-propylene glycol monomethyl ether: integration of pharmacokinetic and developmental toxicity assess...	2003	Carney, E. W.; Pottenger, L. H.; Johnson, K. A.; Liberacki, A. B.; Tornesi, B.; Dryzga, M. D.; Hansen, S. C.; Breslin, W. J.	Toxicol Sci
0.557		✓	s5	4-Hydroxybenzyl modification of the highly teratogenic retinoid, 4-[(1E)-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-1-propen-1-yl]b enzoic acid (...	2011	Anding, A. L.; Nieves, N. J.; Abzianidze, V. V.; Collins, M. D.; Curley, R. W.; Jr.,Clagett-Dame	Chem Res Toxicol
0.668		✓	s3	Initial submission: ortho-phenylphenol: gavage teratology study in new zealand white rabbits (final report) with cover letter dated 062392	1992		Epa/Ots
0.655		✓	s23	A developmental toxicity study of tretinoin administered topically and orally to pregnant Wistar rats	1997	Seegmiller, R. E.; Ford, W. H.; Carter, M. W.; Mitala, J. J.; Powers, W. J.	J Am Acad Dermatol
0.761		✓	s21	The developmental toxicity of ethylene glycol in rats and mice	1985	Price, C. J.; Kimmel, C. A.; Tyl, R. W.; Marr, M. C.	Toxicol Appl Pharmacol
0.599		✓	s20	Teratogenesis of calcium valproate in rabbits	1986	Petrere, J. A.; Anderson, J. A.; Sakowski, R.; Fitzgerald, J. E.; e la Iglesia, F. A.	Teratology
0.687		✓	s2	Initial submission: developmental toxicity of ethylene glycol in rats, with cover letter dated 050792	1992		Epa/Ots
0.73		✓	s19	De...	1995	Neeper-Bradley, T. L.; Tyl, R. W.; Fisher, L. C.; Kubena, M. F.; Vrbanic, M. A.; Losco, P. E.	Fundam Appl Toxicol
0.653		✓	s18	Me...	1983	Minsker, D. H.; MacDonald, J. S.; Robertson, R. T.; Bokelman, D. L.	Teratology
0.8...		✓	s17	Rep...	2007	McClain, R. M.; Wolz, E.; Davidovich, A.; Edwards, J.; Bausch, J.	Food Chem Toxicol
0.835		✓	s15	Ter...	1988	Infurna, R.; Levy, B.; Meng, C.; Yau, E.; Traina, V.; Rolofson, G.; Stevens, J.; Barnett, J.	J Toxicol Environ Health
0.681		✓	s13	Non...	1996	Greene, J. A.; Ayers, K. M.; Tucker, W. E.; Jr.,de Miranda	Fundam Appl Toxicol
0.649		✓	s12	Pre...	1968	Fritz, H.; Hess, R.	Experientia
0.69		✓	s11	Dev...	1993	Field, E. A.; Price, C. J.; Sleet, R. B.; George, J. D.; Marr, M. C.; Myers, C. B.; Schwetz, B. A.; Morrissey, R. E.	Teratology
0.668		✓	s10	Dev...	2004	Daston, G. P.	Birth Defects Res B Dev Reprod Toxicol
0.513		✓	h999431	Ter...	1989	Giavini, E.; Broccia, M. L.; Prati, M.; Cova, D.; Rossini, L.	Bulletin of Environmental Contamination and Tox

3. Use lowest ranked "test" study as cut-off, send studies scoring 0.42 and above to screen

Iterative Search String Tests to Help Determine Approach

Test	Result	Meaning
SS1 vs. SS2	SS1<SS2	SS1 might be a better approach
SS+Chemical vs. PubMed&Chemical	SS+Chem ~ PubMed&Chemical Search	SS might be too broad
SS+Chemical and On-topic PMIDs	SS+Chemical identifies all or most PMIDs	Likely good

Tags-Examples

Included

What kind of evidence stream?

☐ Human ☐ Animal (mammalian model) ☐ in vitro

Which health outcomes apply?

☐ acute Toxicity/Poisoning

☐ ADME/toxicokinetic

☐ body weight

☐ cancer

☐ cardiovascular

☐ clinical chemistry/biochemical/cytotoxicity/cellular function

☐ endocrine (hormone)

☐ gastrointestinal

☐ gene expression/omics

☐ genotoxicity

Supplemental

What kind of supplemental material?

☐ non-inhalation route

☐ MOA/mech (cancer)

☐ MOA/mech (non-cancer)

☐ in vitro

☐ ADME/toxicokinetic-related

☐ case report

☐ mixture/cigarette smoke

☐ exposure characterization (no health outcome)

☐ susceptible population

☐ in silico/modeled

☐ ecotox/non-mammalian model

☐ other

Excluded

If reference is excluded, please indicate the reason:

☐ not relevant to PECO

☐ review, commentary, or letter with no original data

☐ conference abstract or thesis (or unpublished data)

☐ unable to obtain full-text

☐ not relevant to PECO, but has supplemental material

These data that can be tracked and visually displayed.

Use of Artificial Intelligence for Literature Screening

Lyle D. Burgoon, Ph.D.

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US Army Engineer Research and Development Center

Environmental Laboratory

Opinions expressed are those of the author and do not necessarily reflect US Army policy.

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Engineer Research and Development Center

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Innovative solutions for a safer, better world

Objectives for Talk

- Challenges in using AI for literature screening

- How we normally do this

- Thoughts on AI performance (and what to look for)

- Temper user expectations in the near term

Objective: Literature Screening

- Lots of papers

- Quickly get rid of irrelevant ones

- Don't want to miss relevant papers

- Operationally this means (true for all screening apps):
    - Accept false positives
    - Require low false negative rate

How Do We Teach Computers?

- Focus on supervised methods
  - Tell the computer what papers <u>we want</u> vs <u>don't want</u>

How Do We Teach Computers
This Paper, Not That Paper

- If chemical or stressor-specific screening
  - Grab a bunch of papers at random
  - Screen by hand and label
    - Relevant vs not relevant
  - Machine Learning
    - Assess performance using k-fold cross-validation
    - Looking for high specificity and high true positive rate
    - You want to tolerate false positives

How Do We Teach Computers
This Paper, Not That Paper

- If general screening (not specific to a chemical or stressor)
  - Be prepared
    - You will need a lot of papers that are hand-screened that span multiple chemicals or stressors
  - Grab a bunch of papers at random
  - Screen by hand and label
    - Relevant vs not relevant
  - Machine Learning
    - Assess performance using k-fold cross-validation
    - Looking for high specificity and high true positive rate
    - You want to tolerate false positives

What Is the Computer Modeling?

- TF-IDF: Term frequency-inverse document frequency

- Term frequency (TF)

$$TF = \frac{number\_of\_times\_term\_occurrs}{total\_words\_document}$$

- Inverse document frequency (IDF)

$$IDF = \log\left(\frac{total\_number\_documents}{number\_documents\_with\_term}\right)$$

- TF-IDF:

$$\text{TF-IDF} = TF * IDF$$

Example

- Screen papers on 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)
- All papers have "TCDD" in them
- 500 papers
- TC-IDF will = 0
- Algorithm not likely to use "TCDD"

$$IDF = \log\left(\frac{total\_number\_documents}{number\_documents\_with\_term}\right)$$

$$IDF = \log\left(\frac{500}{500}\right) = \log(1) = 0$$

$$TF\text{-}IDF = IDF * 0 = 0$$

What Will ML Algorithm Do?

- "Looking" for patterns of term occurrences based on TF-IDF

- Different algorithms work different ways

    - Random Forest

    - Support Vector Machines

    - Naïve Bayes

Caveats

- Classification models don't extrapolate well
  - If paper X is vastly different from papers in the training set this won't work well
    - Classifying an article from The Daily Beast, BBC News, Washington Post... (or name your favorite news source)
    - Model: trained on scientific papers
    - Outcome: ????
  - Why?
    - The word usage is likely to be very different
      - Word frequency will be very different
      - Model may respond in an unpredictable manner

Caveats

- Machine learning algorithms are like toddlers
  - It models the world based on the information you give it
  - If you only ever show a toddler:
    - Green apples
    - Red tomatoes
  - Be prepared for
    - Red apple = tomato (in toddler world)
    - Green tomato = green apple (in toddler world)
    - Breaking that association takes a lot of new evidence and retraining

Caveats

- Unbalanced data
  - Typically
    - Relevant papers < non-relevant papers
  - Solution
    - Undersampling (non-relevant papers) + Bagging
    - Oversampling (relevant papers) + Bagging

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Development of a BioPortal Ontology Lookup tool

by Kellie Fay
Systematic Review in Exposure Science Summit
04/25/2019

Ontologies

- An agreed upon knowledge representation about a subject
  - Provides a hierarchy of concepts/terms (classes) within the subject domains
  - Describes the relationships among the classes
    - Data are stored as *triples*
    - Subject-predicate-object
    - *Berlin is the capital of Germany*
  - Human and computer readable
  - Usually depicted as a graphical relationship
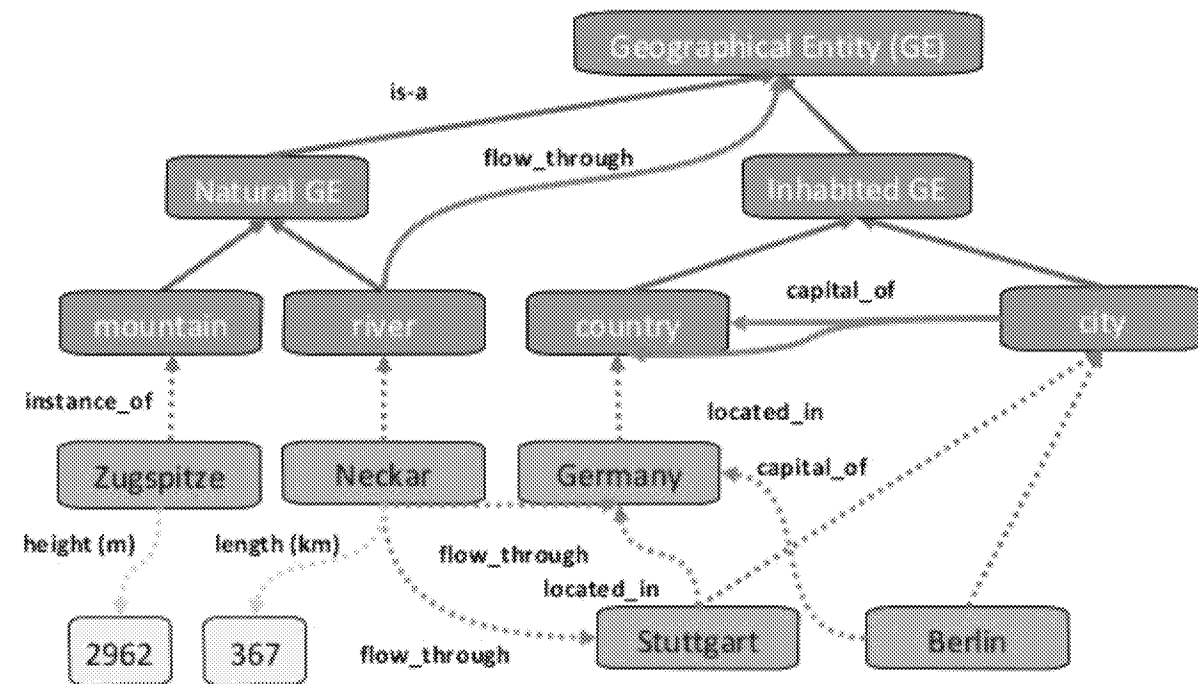
Ontologies

- The bio-medical field is the most advanced in employing ontologies

Gene ontology (GO) most widely used/recognized

Other ontologies are being developed to describe
toxicology and exposure sciences:
ChEBI – Chemical Entities of Biological Interest
ENVO – Environment Ontology
EXO – Exposure Ontology
BAO – Bioassay Ontology
CHEAR – Children's Health Exposure Analysis Resource
OBI – Ontology for biomedical investigations
ECTO – Environment Conditions and Treatments
ontology PhenX – PhenX Phenotypic Terms Ontology
(extends exposure ontoloties)
GO-CAMs – Gene Ontology - Causal Activity Model
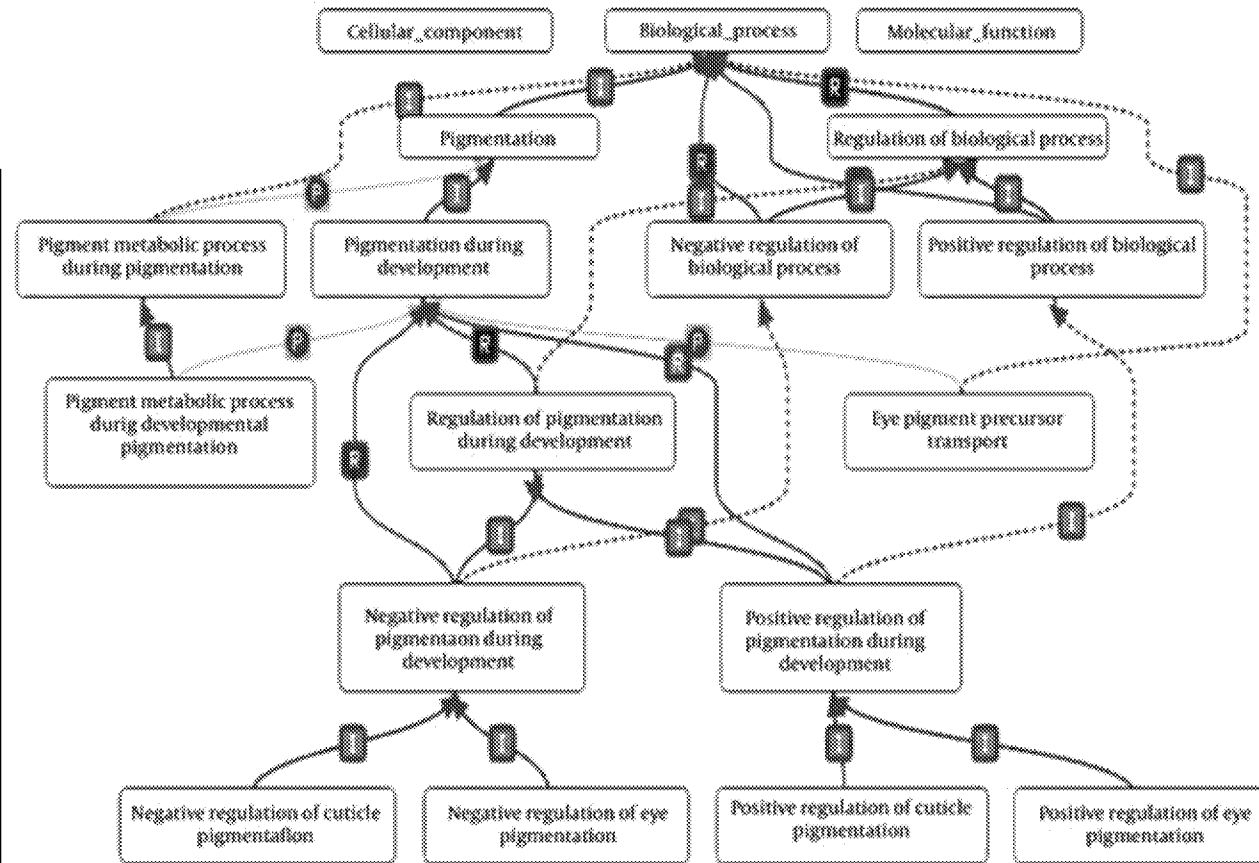
Applications

- Improved database querying
  - UniProt
  - Cochrane Database of Systematic Reviews – see Mavergames et al., (2013)
    - Took a legacy database of systematic reviews of clinical results – using PICO framework
    - Developed an ontology to model the system

- Computational Predictions
  - Predict drugs as disease treatments
  - Cross-species effects predictions (read across) to predict mechanism/genetic source or rare diseases

- Text mining
  - To inform systematic reviews
    - SWIFT review
  - To semi-automate data import

BioPortal

BioPortal Ontology Browser https://bioportal.bioontology.org
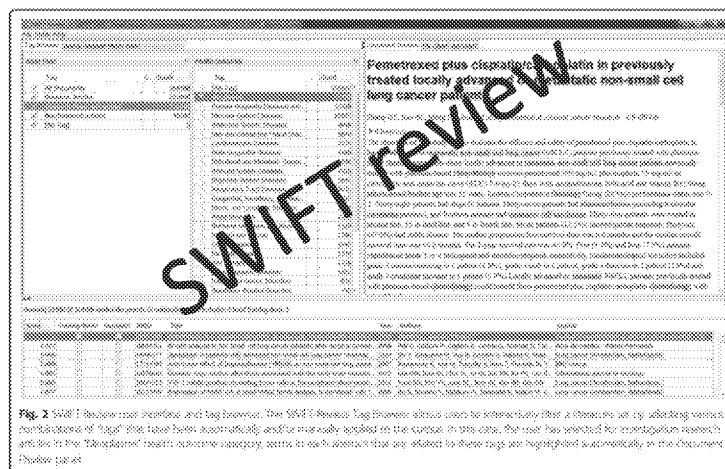
- 694 curated biological ontologies
- ~10 million ontology classes
- Annotator feature - matches ontology classes to input terms
- Recommender feature - Customizable algorithm for scoring specific ontologies based on **coverage**, **acceptance**, **detail** and **specialization**
- SPARQL endpoint – RDF serializations of:
  - Ontology content
  - Ontology metadata (ontology context, creation date, version, format, etc)
  - Ontology mappings
    - User submitted
    - Automated
- Representational State Transfer (REST API)

BioPortal

BioPortal Ontology Browser

- Website allows user to query a term (or a paragraph) to find all ontologies (or selected ontologies) with a matching class

  BUT!

- No batch term processing

- To retrieve an ontology class identifier for a term (i.e., ECOTOX Code), the user must explore the linked site for each individual ontology separately

- Difficult to understand context for each match

BioPortal Lookup tool

- Java-based tool that uses the REST web service API

- Allows for batch processing and makes use of BioPortal's Annotator and Recommender features

- Returns information from each matched ontology- drills down into each ontology result for details
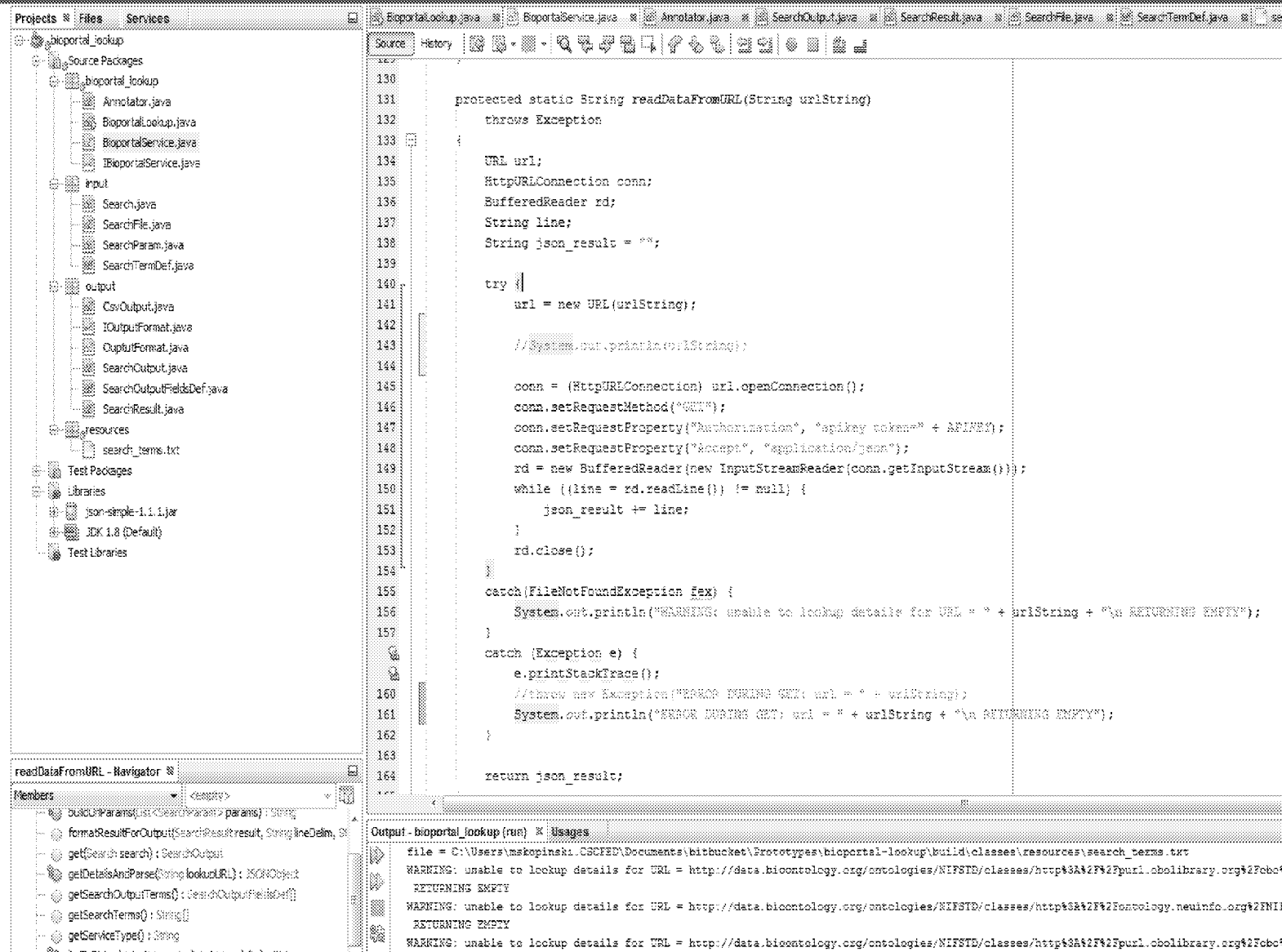
Mapping terms to ontology classes

Input = text file of search terms (ECOTOX codes)

search_terms_Meas1.txt - Notepad

File   Edit   Format   View   Help

Biomass
Normal
Survival
Progeny counts/numbers
Length
Food consumption
Organ weight in relationship to body weight
Population growth rate
Immobile
Damage
Abnormal
Germination
Growth, general
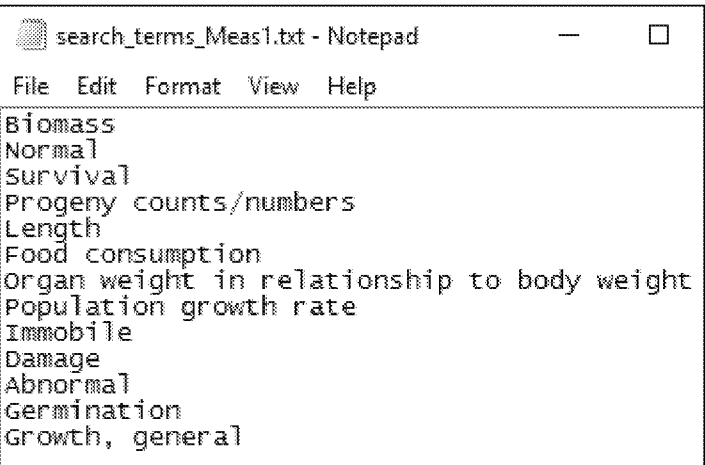
Command line application
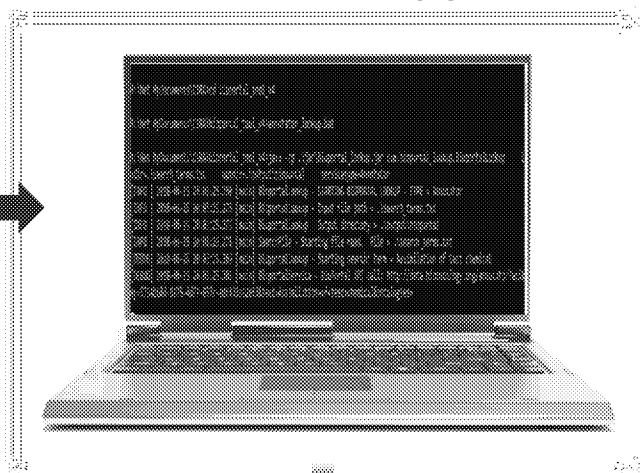
Output = CSV file of matched Ontology classes and details

Search Parameters	Matched Class	Matched Ontology	Preferred Name	Synonyms	Definition	Ont. ID
input=Biomass	biomass	The Ecosystem Ontology	Biomass	biomatter	Biomass is organic matter derived from living, or recently living organ	http://purl.dataone.org/odo/ECSO_00001114
input=Biomass	biomass	Gene Regulation Ontology	biomass			http://www.bootstrep.eu/ontology/GRO#Biomass
input=Biomass	organic material	Environment Ontology	organic material	biomass	Environmental material derived from living organisms.	http://purl.obolibrary.org/obo/ENVO_01000155
input=Biomass	organic material	Children's Health Exposure A	organic material	biomass	Environmental material derived from living organisms.	http://purl.obolibrary.org/obo/ENVO_01000155
input=Biomass	organic material	eNanoMapper	organic material	biomass	Environmental material derived from living organisms.	http://purl.obolibrary.org/obo/ENVO_01000155
input=Biomass	organic material	GenEpiO	organic material	biomass	Environmental material derived from living organisms.	http://purl.obolibrary.org/obo/ENVO_01000155
input=Normal	Normal	National Cancer Institute The	Normal	NORMAL	Being approximately average or within certain limits; conforming wit	http://ncicb.nci.nih.gov/xml/owl/EVS/Thesaurus.o
input=Normal	normal	Mass Spectrometry Ontology	normal	average	A quality inhering in a bearer by virtue of the bearer's exhibiting no d	http://purl.obolibrary.org/obo/PATO_0000461
input=Normal	normal	Ascomycete Phenotype Ontc	normal	wild type	The observed phenotype shows no detectable difference between t	http://purl.obolibrary.org/obo/APO_0000117
input=Normal	normal	Obstetric and Neonatal Onto	normal	average	A quality inhering in a bearer by virtue of the bearer's exhibiting no d	http://purl.obolibrary.org/obo/PATO_0000461

BioPortal Lookup tool version control

- Ontologies necessarily evolve to reflect new knowledge and the technology is being applied to new fields

- BioPortal Lookup Tool provides an update feature
  - Internal database store to compare output of a new run with most recent run
  - Read-in file capability to compare output of a new run with a previous output file

	A	B	C	D	E
1	Input Term	Matching Term	Ontology Acronym	Ontology ID	STATUS
2	Assimilation of test chemical		SNOMEDCT	http://purl.bioontology.org/ontology/STY/T103	NEW
3	Ratio		HL7	http://purl.bioontology.org/ontology/HL7/C1547037	UNCHANGED
4	Accumulation, general	accumulation	CHEAR	http://purl.obolibrary.org/obo/PATO_0002269	UNCHANGED
5	Translocation	translocation	GENO	http://purl.obolibrary.org/obo/SO_0000199	UNCHANGED
6	Body concentration	concentration of	CCONT	http://purl.obolibrary.org/obo/PATO_0000033	UNCHANGED
7	Assimilation efficiency	efficiency	NIFDYS	http://purl.obolibrary.org/obo/PATO_0001029	UNCHANGED
8	Lethal body concentration	multicellular organism	CHEAR	http://purl.obolibrary.org/obo/UBERON_0000468	UNCHANGED
9	Assimilation of test chemical		SWEET	http://sweetontology.net/reprDataServiceAnalysis/Assimilation	NEW
10	Assimilation of test chemical		VANDF	http://purl.bioontology.org/ontology/STY/T103	UNCHANGED
11	Assimilation of test chemical		UBERON	http://purl.bioontology.org/ontology/STY/T103	REMOVED

Summary

1) The BioPortal Lookup tool is easy to use and customizable
    1) Reads in simple text input files
    2) Makes use of all features of the BioPortal ontology browser website
    3) Query all BioPortal ontologies or select ontologies

2) Returns information that would require extra steps on the BioPortal site and maps better than online tool

3) Allows for updates over time as ontologies are eliminated/added/ modified

4) Provides output as .CSV files

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GDIT
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Anne Pilli
Brian Kinziger
Stephen Erickson

Using Endnote Software to Identify and Retrieve Key Pesticide Epidemiological Studies

EPA OCSPP Presentation for Systematic Review in Exposure Science Summit

Ashlee Aldridge, Epidemiologist
Office of Pesticides, Health Effects Division
U.S. Environmental Protection Agency

Epidemiology Assessment Approach in OPP

- Tiered reviews are guided by Office of Pesticides Programs' (OPP's) Epidemiological Framework published in 2016

- Emphasizes study quality and weight of evidence

- "Fit for purpose"

- Required resources are "matched" or balanced against any anticipated or expected information gain from further, more in-depth research

Office of Pesticide Programs'
Framework for Incorporating
Human Epidemiologic & Incident Data in
Risk Assessments for Pesticides

December 28, 2016

Office of Pesticide Programs
US Environmental Protection Agency
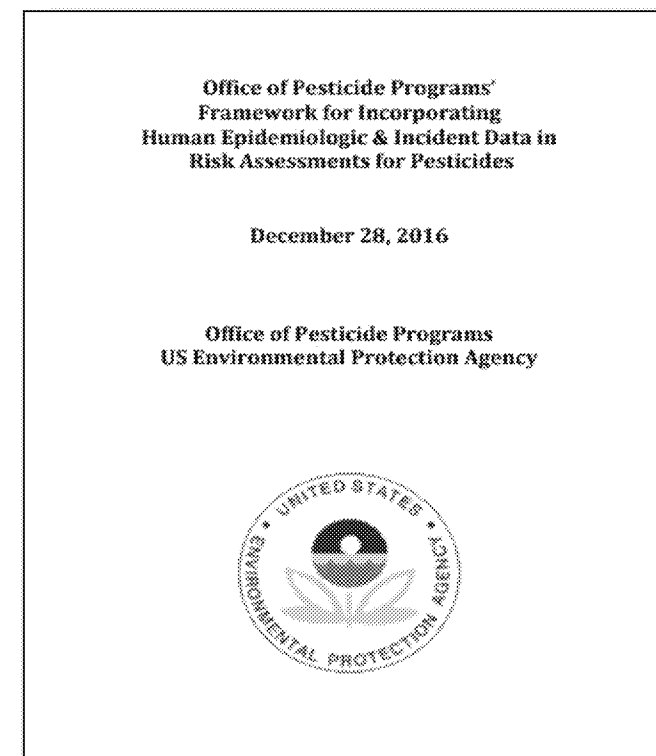
Tiered Review Approach

- EPA's Office of Pesticide Programs (OPP) has adopted a tiered assessment approach to fulfill its regulatory mandate and respond to emerging public health issues.

  - Manage program workload

  - Prioritize potential risk issues that warrant systematic investigation

Tier III

Tier II

Tier I

Resources   Public Health Significance

ED_004465_00012138-00099
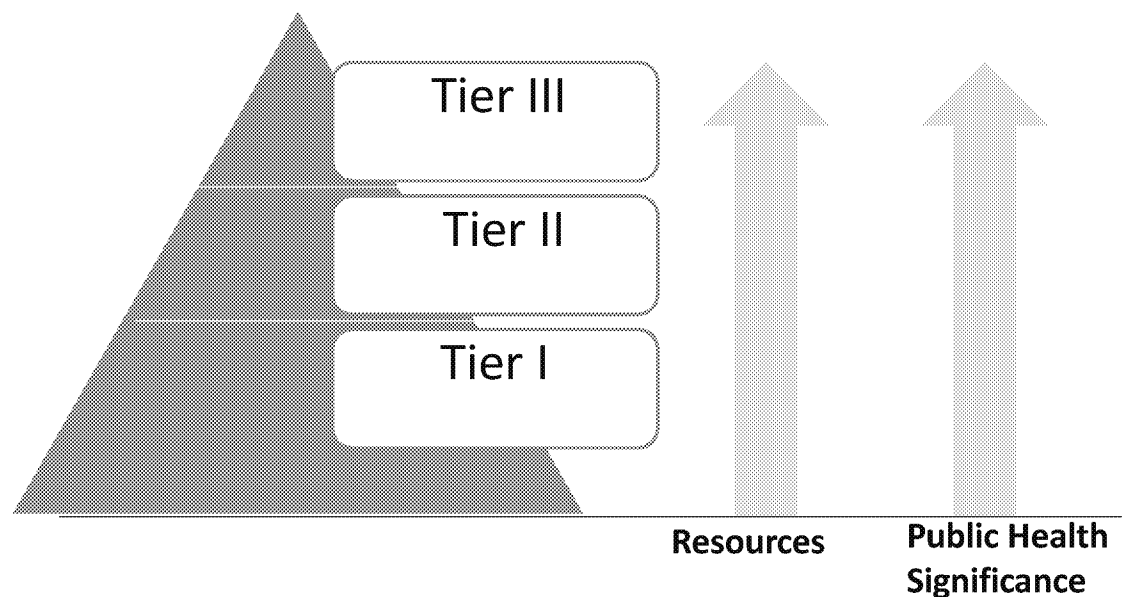
Tier I, Tier II, & Tier III Epidemiology Reviews In OPP

- **Tier I: Update to scoping exercise**

  - Research and evaluation generally limited to Agriculture Health Study (AHS)-related publications

- **Tier II and Tier IIIs: Systematic review + multi-disciplinary integration**

  - Broader search of epidemiologic literature including comprehensive data collection and systematic literature review

  - Can involve more comprehensive epidemiologic methods

Using EndNote Software for Epidemiology Reviews

- EndNote is a reference management software used to file, sort, and find articles

- EndNote acts as a 'repository' for all OPP articles of interest

- OPP has created an 'AHS Library' within EndNote - useful for Tier I Review

    - AHS Library in EndNote contains all AHS studies for OPP pesticides involved in past risk assessments
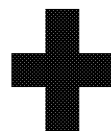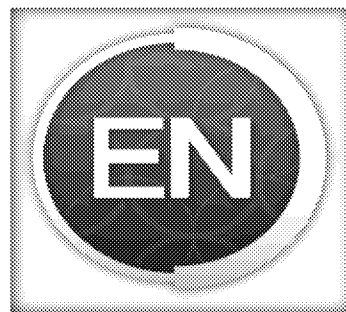
Why use EndNote for AHS articles?

- EndNote is useful for several reasons:

  - Locates corresponding PDF with AHS reference

  - Quickly searches full-text articles (not just abstract) to determine if select pesticides are related to specific health outcomes

  - Multiple team members can utilize the EndNote database simultaneously; can be used for several projects

  - Creates references for individual studies

  - Filing and sorting several AHS articles

EndNote X7 - [Full AHS library_2.2.17.eni]

File   Edit   References   Groups   Tools   Window   Help

Annotated

Quick Search   Hide Search Panel

My Library

All References	(485)
Search Re...	(43)
Unfiled	(221)
Trash	(8)

My Groups

2,4-D AHS studies	(31)
AHS library (17?)	(2??)
Bifenthrin	(2)
Cyfluthrin	(6)
Cyhalothrin	(1)
Cypermethrin	(4)
Deltamethrin	(3)
Esfenvalerate	(4)
Fenpropathrin	(1)
Fenvalerate	(5)
Pendimethalin	(0)
Pyrethrins	(5)

Online Search

Library of Congress	(0)
LISTA (EBSCO)	(0)
PubMed (NLM)	(0)
Web of Science (TS)	(0)

more...

Find Full Text

Search   Options

Search Whole Group   Match Case   Match Words

Any Field + PDF with Notes	Contains		
And	Any Field + PDF with Notes	Contains	
And	Title	Contains	

			Author	Year	Title	Rating	Journal	Last Updated	Refer
			Alavanja, M. C.; Sandler, D. P.; Lynch, ...	2005	Cancer incidence in the agricultural health study		Scand J Wo...	2/13/2017	Journ
			Alavanja, M. C.; Sandler, D. P.; McDon...	1998	Factors associated with self-reported, pesticide-related visits to health care providers in the agric...		Environ He...	2/13/2017	Journ
			Alavanja, M. C.; Sandler, D. P.; McDon...	1999	Characteristics of pesticide use in a pesticide applicator cohort: the Agricultural Health Study		Environ Res	2/13/2017	Journ
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			Alavanja, M. C.; Sprince, N. L.; Oliver, ...	2001	Nested case-control analysis of high pesticide exposure events from the Agricultural Health Study		Am J Ind M...	2/13/2017	Journ
			Alavanja, M. C.; Ward, M. H.; Reynold...	2007	Carcinogenicity of agricultural pesticides in adults and children		J Agromedi...	2/23/2017	Journ
			Alexander, Melannie; Koutros, Stella;...	2017	Pesticide use and LINE-1 methylation among male private pesticide applicators in the Agricultur...		Environme...	12/1/2017	Journ
			Andreotti, G.; Freeman, L. E.; Hou, L.;...	2009	Agricultural pesticide use and pancreatic cancer risk in the Agricultural Health Study Cohort		Int J Cancer	2/14/2017	Journ
			Andreotti, G.; Hoppin, J. A.; Hou, L.; ...	2015	Pesticide Use and Relative Leukocyte Telomere Length in the Agricultural Health Study		PLoS One	2/13/2017	Journ
			Andreotti, G.; Hou, L.; Beane Freema...	2010	Body mass index, agricultural pesticide use, and cancer incidence in the Agricultural Health Stud...		Cancer Cau...	2/13/2017	Journ
			Andreotti, G.; Koutros, S.; Berndt, S. ...	2012	The Interaction between Pesticide Use and Genetic Variants Involved in Lipid Metabolism on Pro...		J Cancer Ep...	2/13/2017	Journ
			Andreotti, G.; Koutros, S.; Hofmann, ...	2017	Glyphosate Use and Cancer Incidence in the Agricultural Health Study		J Natl Canc...	11/16/2017	Journ
			Arem, H.; Yu, K.; Xiong, X.; Moy, K.; F...	2015	Vitamin D metabolic pathway genes and pancreatic cancer risk		PLoS One	2/13/2017	Journ
			Bakke, B.; De Roos, A. J.; Barr, D. B.; ...	2009	Exposure to atrazine and selected non-persistent pesticides among corn farmers during a growin...		J Expo Sci E...	2/13/2017	Journ
			Barry, K. H.; Koutros, S.; Andreotti, G...	2012	Genetic variation in nucleotide excision repair pathway genes, pesticide exposure and prostate c...		Carcinogen...	2/13/2017	Journ
			Barry, K. H.; Koutros, S.; Berndt, S. I.;...	2011	Genetic variation in base excision repair pathway genes, pesticide exposure, and prostate cancer ...		Environ He...	2/13/2017	Journ
			Barry, K. H.; Koutros, S.; Lubin, J. H.; ...	2012	Methyl bromide exposure and cancer risk in the Agricultural Health Study		Cancer Cau...	2/13/2017	Journ
			Beane Freeman, L. E.; Bonner, M. R.; ...	2005	Cancer incidence among male pesticide applicators in the Agricultural Health Study cohort expos...		Am J Epide...	2/13/2017	Journ
			Beane Freeman, L. E.; Deroos, A. J.; K...	2012	Poultry and livestock exposure and cancer risk among farmers in the agricultural health study		Cancer Cau...	2/13/2017	Journ
			Beard, J. D.; Hoppin, J. A.; Richards, ...	2013	Pesticide exposure and self-reported incident depression among wives in the Agricultural Health ...		Environ Res	2/13/2017	Journ
			Beard, J. D.; Umbach, D. M.; Hoppin, ...	2011	Suicide and pesticide use among pesticide applicators and their spouses in the agricultural health...		Environ He...	2/13/2017	Journ
			Beard, J. D.; Umbach, D. M.; Hoppin, ...	2014	Pesticide exposure and depression among male private pesticide applicators in the agricultural h...		Environ He...	2/13/2017	Journ
			Bell, E. M.; Sandler, D. P.; Alavanja, M...	2006	High pesticide exposure events among farmers and spouses enrolled in the Agricultural Health S...		J Agric Saf ...	2/13/2017	Journ
			Berndt, S. I.; Wang, Z.; Yeager, M.; Al...	2015	Two susceptibility loci identified for prostate cancer aggressiveness		Nat Commun	2/13/2017	Journ
			Berrington de Gonzalez, A.; Hartge, ...	2010	Body-mass index and mortality among 1.46 million white adults		N Engl J Med	2/13/2017	Journ
			Beseler, C.; Stallones, L.; Hoppin, J. A...	2006	Depression and pesticide exposures in female spouses of licensed pesticide applicators in the agr...		J Occup En...	2/13/2017	Journ
			Beseler, C. L.; Stallones, L.; Hoppin, J...	2008	Depression and pesticide exposures among private pesticide applicators enrolled in the Agricultu...		Environ He...	2/13/2017	Journ
			Black, A.; Gibson, T. M.; Shiels, M. S.; ...	2014	Pooling prospective studies to investigate the etiology of second cancers		Cancer Epid...	2/13/2017	Journ
			Blair, A.; Hines, C. J.; Thomas, K. W.; ...	2015	Investing in prospective cohorts for etiologic study of occupational exposures		Am J Ind M...	2/13/2017	Journ

Showing 253 of 253 references in Group. (All References: 485)

EndNote X7 - [Full AHS library_2.2.17.eni]

File Edit References Groups Tools Window Help

Annotated

Quick Search   Hide Search Panel

My Library	
All References	(485)
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Trash	(8)

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Fenpropathrin	(1)
Fenvalerate	(5)
Pendimethalin	(0)
Pyrethrins	(5)

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LISTA (EBSCO)	(0)
PubMed (NLM)	(0)
Web of Science (TS)	(0)
more...	

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Barry, K. H.; Koutros, S.; Berndt, S. I.;...	2011	Genetic variation in base excision repair pathway genes, pesticide exposure, and prostate cancer ...		Environ He...	2/13/2017	Journ
Barry, K. H.; Koutros, S.; Lubin, J. H.; ...	2012	Methyl bromide exposure and cancer risk in the Agricultural Health Study		Cancer Cau...	2/13/2017	Journ
Beane Freeman, L. E.; Bonner, M. R.; ...	2005	Cancer incidence among male pesticide applicators in the Agricultural Health Study cohort expos...		Am J Epide...	2/13/2017	Journ
Beane Freeman, L. E.; Deroos, A. J.; K...	2012	Poultry and livestock exposure and cancer risk among farmers in the agricultural health study		Cancer Cau...	2/13/2017	Journ
Beard, J. D.; Hoppin, J. A.; Richards, ...	2013	Pesticide exposure and self-reported incident depression among wives in the Agricultural Health ...		Environ Res	2/13/2017	Journ
Beard, J. D.; Umbach, D. M.; Hoppin, ...	2011	Suicide and pesticide use among pesticide applicators and their spouses in the agricultural health...		Environ He...	2/13/2017	Journ
Beard, J. D.; Umbach, D. M.; Hoppin, ...	2014	Pesticide exposure and depression among male private pesticide applicators in the agricultural h...		Environ He...	2/13/2017	Journ
Bell, E. M.; Sandler, D. P.; Alavanja, M...	2006	High pesticide exposure events among farmers and spouses enrolled in the Agricultural Health S...		J Agric Saf ...	2/13/2017	Journ
Berndt, S. I.; Wang, Z.; Yeager, M.; Al...	2015	Two susceptibility loci identified for prostate cancer aggressiveness		Nat Commun	2/13/2017	Journ
Berrington de Gonzalez, A.; Hartge, ...	2010	Body-mass index and mortality among 1.46 million white adults		N Engl J Med	2/13/2017	Journ
Beseler, C.; Stallones, L.; Hoppin, J. A...	2006	Depression and pesticide exposures in female spouses of licensed pesticide applicators in the agr...		J Occup En...	2/13/2017	Journ
Beseler, C. L.; Stallones, L.; Hoppin, J...	2008	Depression and pesticide exposures among private pesticide applicators enrolled in the Agricultu...		Environ He...	2/13/2017	Journ
Black, A.; Gibson, T. M.; Shiels, M. S.; ...	2014	Pooling prospective studies to investigate the etiology of second cancers		Cancer Epid...	2/13/2017	Journ
Blair, A.; Hines, C. J.; Thomas, K. W.; ...	2015	Investing in prospective cohorts for etiologic study of occupational exposures		Am J Ind M...	2/13/2017	Journ

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Alavanja, M. C.; Sandler, D. P.; McDon...	1998	Factors associated with self-reported, pesticide-related visits to health care providers in the agric...		Environ He...	2/13/2017	Journ
Alavanja, M. C.; Sandler, D. P.; McDon...	1999	Characteristics of pesticide use in a pesticide applicator cohort: the Agricultural Health Study		Environ Res	2/13/2017	Journ
Alavanja, M. C.; Sandler, D. P.; McMas...	1996	The Agricultural Health Study		Environ He...	2/13/2017	Journ
Alavanja, M. C.; Sprince, N. L.; Oliver, ...	2001	Nested case-control analysis of high pesticide exposure events from the Agricultural Health Study		Am J Ind M...	2/13/2017	Journ
Alavanja, M. C.; Ward, M. H.; Reynold...	2007	Carcinogenicity of agricultural pesticides in adults and children		J Agromedi...	2/23/2017	Journ
Alexander, Melannie; Koutros, Stella;...	2017	Pesticide use and LINE-1 methylation among male private pesticide applicators in the Agricultur...		Environme...	12/1/2017	Journ
Andreotti, G.; Freeman, L. E.; Hou, L.;...	2009	Agricultural pesticide use and pancreatic cancer risk in the Agricultural Health Study Cohort		Int J Cancer	2/14/2017	Journ
Andreotti, G.; Hoppin, J. A.; Hou, L.; ...	2015	Pesticide Use and Relative Leukocyte Telomere Length in the Agricultural Health Study		PLoS One	2/13/2017	Journ
Andreotti, G.; Hou, L.; Beane Freema...	2010	Body mass index, agricultural pesticide use, and cancer incidence in the Agricultural Health Stud...		Cancer Cau...	2/13/2017	Journ
Andreotti, G.; Koutros, S.; Berndt, S. ...	2012	The Interaction between Pesticide Use and Genetic Variants Involved in Lipid Metabolism on Pro...		J Cancer Ep...	2/13/2017	Journ
Andreotti, G.; Koutros, S.; Hofmann, ...	2017	Glyphosate Use and Cancer Incidence in the Agricultural Health Study		J Natl Canc...	11/16/2017	Journ
Arem, H.; Yu, K.; Xiong, X.; Moy, K.; F...	2015	Vitamin D metabolic pathway genes and pancreatic cancer risk		PLoS One	2/13/2017	Journ
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Downloading Articles into EndNote

- When a new AHS study becomes publicly available, OPP will search for and upload the article into EndNote

- For some studies, we can directly download the PDF file into EndNote with a click of a button – about 60/40
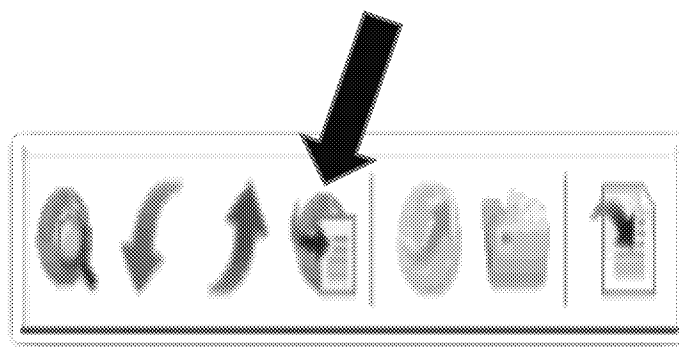
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- Deltamethrin (3)
- Esfenvalerate (4)
- Fenpropathrin (1)
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Blair, A.; Hines, C. J.; Thomas, K. W.; ...	2015	Investing in prospective cohorts for etiologic study of occupational exposures	

Reference | Preview | 🗎 alavanja2005.pdf

Original article

Scand J Work Environ Health 2005;31 suppl 1:39-45

Cancer incidence in the Agricultural Health Study

by Michael CR Alavanja, DrPH, Dale P Sandler, PhD, Charles F Lynch, MD, Charles Knott, MPA, Jay H Lubin, PhD, Robert Tarone, PhD, Kent Thomas, BS, Mustafa Dosemeci, PhD, Joseph Barker, BA, Jane A Hoppin, ScD, Aaron Blair, PhD

Interactive EndNote Example

Managing EndNote

- Quickly searches specific pesticides relative to certain health outcomes

  - Are there any AHS studies on prostate cancer from 2007 - 2015?

  - For permethrin, are there any AHS studies that have been published since 2004?
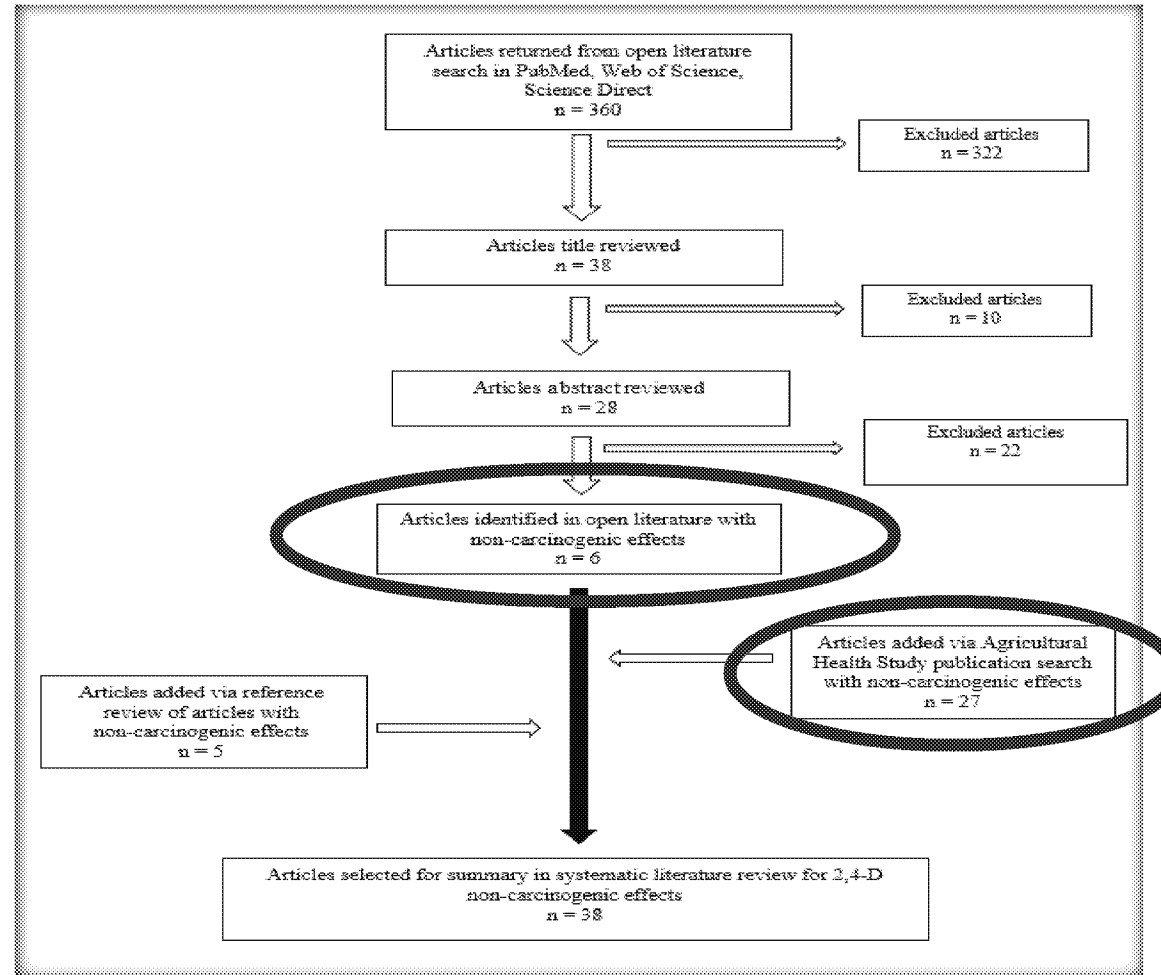
Strengths of EndNote

- Strengths

- Quick tool used for locating AHS articles and <u>full-text</u> searching health outcomes

- Repository for AHS articles

- Citation manager

- Database can be shared with team

- One note of caution:

- When searching within EndNote, you may derive different results when searching by terms

    - Full text search vs. keyword search

General Challenges/Discussion Topics

- Searching via the open literature vs. our EndNote library – yielding a different # of articles – why is this?

- Potential reasons as to why this is occurring:

    - Null vs. significant results – results identified by co-authors vs. papers

    - Abstract vs. full-text searching (i.e. PubMed vs. PubMed Central)

- May decrease the reliability of our results

Ex. 1: Results of Systematic Literature Search for 2,4-D Non-Cancer in Open Literature vs. Endnote Library

Articles returned from open literature search in PubMed, Web of Science, Science Direct
n = 360

Excluded articles
n = 322

Articles title reviewed
n = 38

Excluded articles
n = 10

Articles abstract reviewed
n = 28

Excluded articles
n = 22

Articles identified in open literature with non-carcinogenic effects
n = 6

Articles added via Agricultural Health Study publication search with non-carcinogenic effects
n = 27

Articles added via reference review of articles with non-carcinogenic effects
n = 5

Articles selected for summary in systematic literature review for 2,4-D non-carcinogenic effects
n = 38

Ex. 3 Results of Systematic Literature Search for Atrazine in Open Literature vs. EndNote Library

Articles returned from open literature search in PubMed, Web of Science, Science Direct
n = 1,326

Duplicates removed (n = 66)

Articles title reviewed
n = 1,260

Articles excluded (n = 1,095)

Articles abstract reviewed
n = 165

Articles excluded (n = 86)

Articles full text reviewed
n = 79

Articles excluded (n = 30)

Articles identified in open literature search retained
n = 49

Articles added via Agricultural Health Study publication search
n = 39

Articles added via reference review of articles selected for inclusion
n = 5

Articles selected for summary in systematic literature review
n = 93 (42 reporting carcinogenic and 52 reporting noncarcinogenic outcomes, not mutually exclusive)

Ex. 2 OPP Code for 2,4-D Systematic Literature Search

Database	Search Strategy	Search Date	Articles Returned
Web of Science	(TS=(("2,4-Dichlorophenoxyacetic Acid" OR "2,4-D" OR "2,4-D, diethanolamine salt" OR "2,4-D, dimethylamine salt" OR "2,4-D, isopropylamine salt" OR "2,4-D, triisopropanolamine salt" OR "2,4-D, butoxyethyl ester" OR "2,4-D, 2-ethylhexyl ester" OR "2,4-D, isopropyl ester") AND (human AND (epidemiologic stud* OR cohort* OR case control* OR case-control* OR cross section* OR cross-section* OR cluster* OR environmental exposure* OR occupational exposure* OR ecologic stud* OR aggregate stud*))))	3/16/17	101
Science Direct	("2,4-Dichlorophenoxyacetic Acid" OR "2,4-D" OR "2,4-D, diethanolamine salt" OR "2,4-D, dimethylamine salt" OR "2,4-D, isopropylamine salt" OR "2,4-D, triisopropanolamine salt" OR "2,4-D, butoxyethyl ester" OR "2,4-D, 2-ethylhexyl ester" OR "2,4-D, isopropyl ester") AND (human AND (epidemiologic stud* OR cohort* OR case control* OR case-control* OR cross section* OR cross-section* OR cluster* OR environmental exposure* OR occupational exposure* OR ecologic stud* OR aggregate stud*)) AND NOT ("Agent Orange") .	3/16/17	113
PubMed	"2,4-Dichlorophenoxyacetic Acid"[Mesh] OR "2,4-D amine" [Supplementary Concept] OR "butoxyethanol ester of 2,4-dichlorophenoxyacetic acid" [Supplementary Concept] OR "2-ethylhexyl 2,4-dichlorophenoxyacetate" [Supplementary Concept] OR (2,4-D OR "2,4-D, diethanolamine salt" OR "2,4-D, isopropylamine salt" OR "2,4-D, triisopropanolamine salt" OR "2,4-D, isopropyl ester")) AND (human AND (epidemiologic stud* OR cohort* OR case control* OR case-control* OR cross section* OR cross-section* OR cluster* OR environmental exposure* OR occupational exposure* OR ecologic stud* OR aggregate stud*)) NOT "Agent Orange" [Supplementary Concept] Sort by: Author Filters: Full text; Humans	3/16/17	161

Ex. 3 OPP Code for Atrazine Systematic Literature Search

Database	Search Strategy	Search Date	Articles Returned
Web of Science	TS=((atrazine OR simazine OR propazine OR chlorotriazine* OR aatrex OR atranex OR crisazina OR milo-pro OR prozinex OR gesatop OR princep) AND human AND (health OR epidemiologic stud* OR epidemiol* OR cohort* OR case control* OR case-control* OR cross section* OR cross-section* OR cluster* OR environmental exposure* OR occupational exposure* OR ecologic stud* OR aggregate stud* OR ecological stud*))	1/11/2017	246
Science Direct	(atrazine[MeSH Major Topic] OR simazine[MeSH Major Topic] OR atrazine OR aatrex OR atranex OR crisazina OR simazine OR gesatop OR propazine OR milo-pro OR prozinex OR princep OR chlorotriazine* AND (health OR epidemiologic stud* OR epidemiol* OR cohort* OR case control* OR case-control* OR cross section* OR cross-section* OR cluster* OR environmental exposure* OR occupational exposure* OR ecologic stud* OR aggregate stud*)) AND "humans"[MeSH Terms]	1/11/2017	239
PubMed	(atrazine OR simazine OR propazine OR chlorotriazine*) and (health OR epidemiol* OR cohort* OR "case control*" OR case-control* OR "cross section*" OR cross-section* OR cluster* OR occupational exposure* OR ecologic stud* OR aggregate stud*) and not TITLE(mouse OR mice OR biodegradation OR rice OR immunoassay OR vitro OR fish OR zebrafish OR bovine OR turtle OR crab OR crayfish OR ring OR carp OR alfalfa OR swine OR pig OR fate OR transport OR salamander OR trout OR polymer OR titanium OR catfish OR rodent OR dam OR dams OR diamond OR clay OR pathway OR production OR expression OR sorption OR review OR larva* OR chromatograph* OR spectrometr* OR nanopart* OR bioremed* OR animal* OR mussel* OR quail* OR rat* OR validat* OR cytomet* OR biopurificat* OR immunosens* OR alga* OR microalg* OR degrad* OR biodegrade* OR gravimeter* OR effluent* OR tadpole* OR imputat* OR adsorpt* OR transformat* OR oxidat* OR kinetic* OR photoactive* OR snail* OR electrod* OR pharmacokinet* OR spectra* OR microsom* OR biosens* OR model* OR immunobiosens*)	1/11/2017	841

PubMed vs. PubMed Central (PMC)

Database	Search Strategy	Total Articles Returned	AHS Articles Returned
PubMed	"2,4-Dichlorophenoxyacetic Acid"[Mesh] OR "2,4-D amine" [Supplementary Concept] OR "butoxyethanol ester of 2,4-dichlorophenoxyacetic acid" [Supplementary Concept] OR "2-ethylhexyl 2,4-dichlorophenoxyacetate" [Supplementary Concept] OR (2,4-D OR "2,4-D, diethanolamine salt" OR "2,4-D, isopropylamine salt" OR "2,4-D, triisopropanolamine salt" OR "2,4-D, isopropyl ester")) AND (human AND (epidemiologic stud* OR cohort* OR case control* OR case-control* OR cross section* OR cross-section* OR cluster* OR environmental exposure* OR occupational exposure* OR ecologic stud* OR aggregate stud*)) NOT "Agent Orange" [Supplementary Concept] Sort by: Author Filters: Full text; Humans	161	6
PubMed Central	(("2,4-Dichlorophenoxyacetic Acid"[mh] OR "2,4-Dichlorophenoxyacetic Acid"[tw]) OR "2,4-D amine" [Supplementary Concept] OR "2,4-dichlorophenoxyacetic acid isoctyl ester" [Supplementary Concept] OR "2,4-D n-butyl ester" [Supplementary Concept] OR "2,4-dichlorophenoxyacetic acid propylene glycol butyl ether ester" [Supplementary Concept] OR "2,4-di(n-undecylamino)-6-amino-1,3,5-triazine-melamine" [Supplementary Concept] OR "2,4-dichlorophenoxyacetic acid oxygenase class III" [Supplementary Concept] OR "2,4-diamino-5-(3-bromo-4,5-dimethoxybenzyl)pyrimidine" [Supplementary Concept] OR "2,4-diamino-5-(4-ethoxy-3,5-dimethoxybenzyl)pyrimidine" [Supplementary Concept] OR "2,4-dichlorophenoxyacetate-alpha-ketoglutarate dioxygenase" [Supplementary Concept] OR "2,4-dichlorophenoxyacetic acid methyl ester" [Supplementary Concept] OR "2,4-dichlorophenoxyacetic acid monooxygenase" [Supplementary Concept] OR "butoxyethanol ester of 2,4-dichlorophenoxyacetic acid" [Supplementary Concept] OR (2,4-D[tw] OR "2,4-D diethanolamine salt"[tw] OR "2,4-D isopropylamine salt"[tw] OR "2,4-D triisopropanolamine salt"[tw] OR "2,4-D isopropyl ester"[tw])) AND (("humans"[mh] OR human*[tw]) AND (("epidemiologic studies"[mh] OR epidemiologic stud*[tw]) OR ("cohort studies"[mh] OR cohort*[tw]) OR ("case-control studies"[mh] OR case control[tw] OR case-control [tw]) OR "cross section*" OR "cross-section*" OR ("cluster analysis"[mh] OR cluster*[tw]) OR ecologic stud* OR aggregate stud* OR ("environmental exposure"[mh] OR "occupational exposure" [mh])) NOT("Agent Orange"[mh])	941	20

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Recap: Results of Systematic Literature Search for 2,4-D Non-Cancer in Open Literature vs. Endnote Library
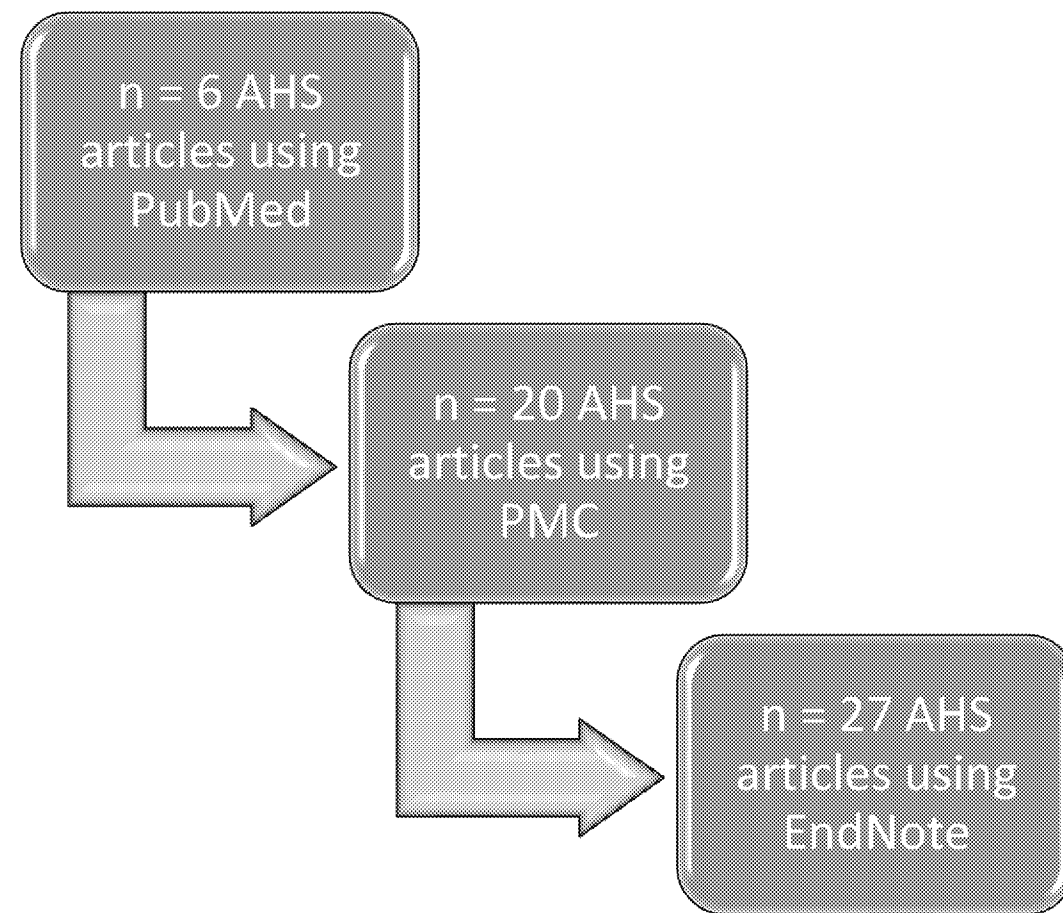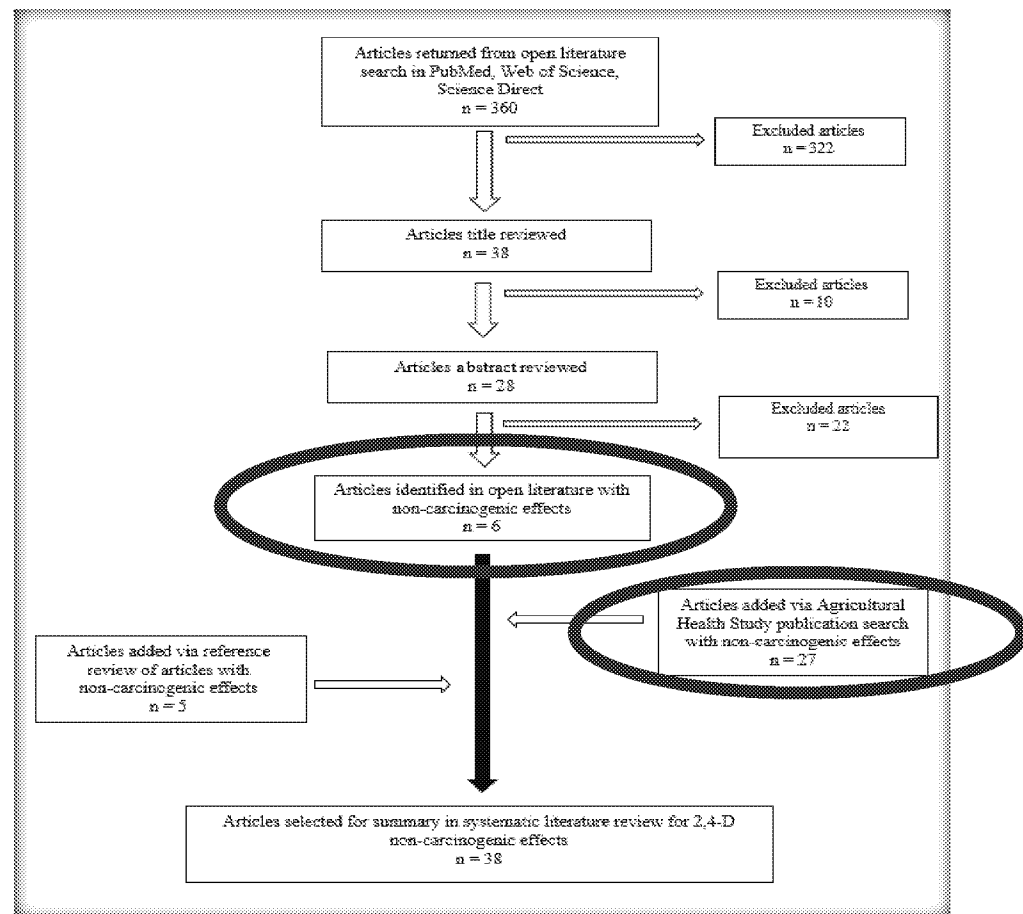
Conclusion

- OPP actively monitors the AHS website to conduct our risk assessments for several pesticides

- EndNote database is a great tool for quickly searching for AHS articles with <u>both</u> null and significant results

- Looking into future use of PMC in addition to EndNote databases for full-text searching

Study Quality Evaluation in IRIS Assessments and Engaging with Exposure Sciences Experts during Systematic Review of Epidemiological Studies

Presented by
Rebecca M. Nachman,
Integrated Risk Information System Division
U.S. Environmental Protection Agency*

*The views expressed in this presentation are those of the author and do not necessarily represent the views or policies of the U.S. Environmental Protection Agency.

Integrated Risk Information System (IRIS)

- Assess human health effects that may result from exposure to chemicals in the environment

- Provide toxicity information used by state, local and federal health agencies, as well as international health organizations

- Maintain and update the IRIS database

Study Evaluation: A Step in the IRIS SR Process
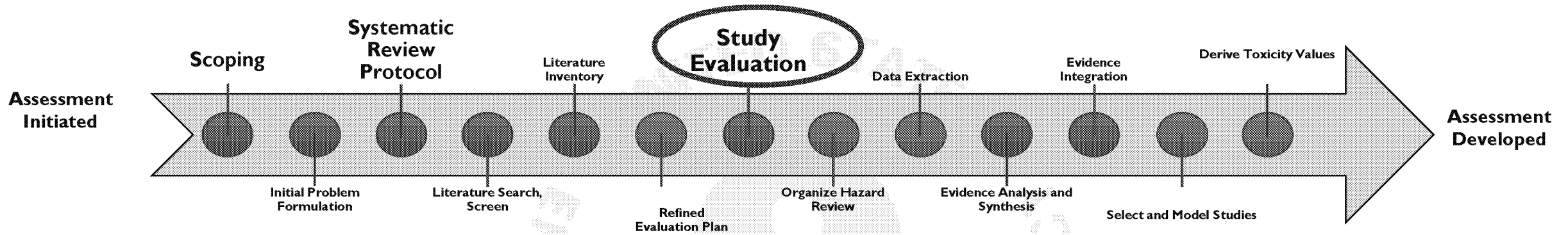
Purpose of Study Evaluation:

- Ensure that the studies used in the assessment were conducted in such a manner that the results are credible

Exposure Measurements and Epidemiologic Evidence: Garbage In, Garbage Out

β = Δ response
per Δ unit exposure

β is estimated

r=0.54
p=0.01*
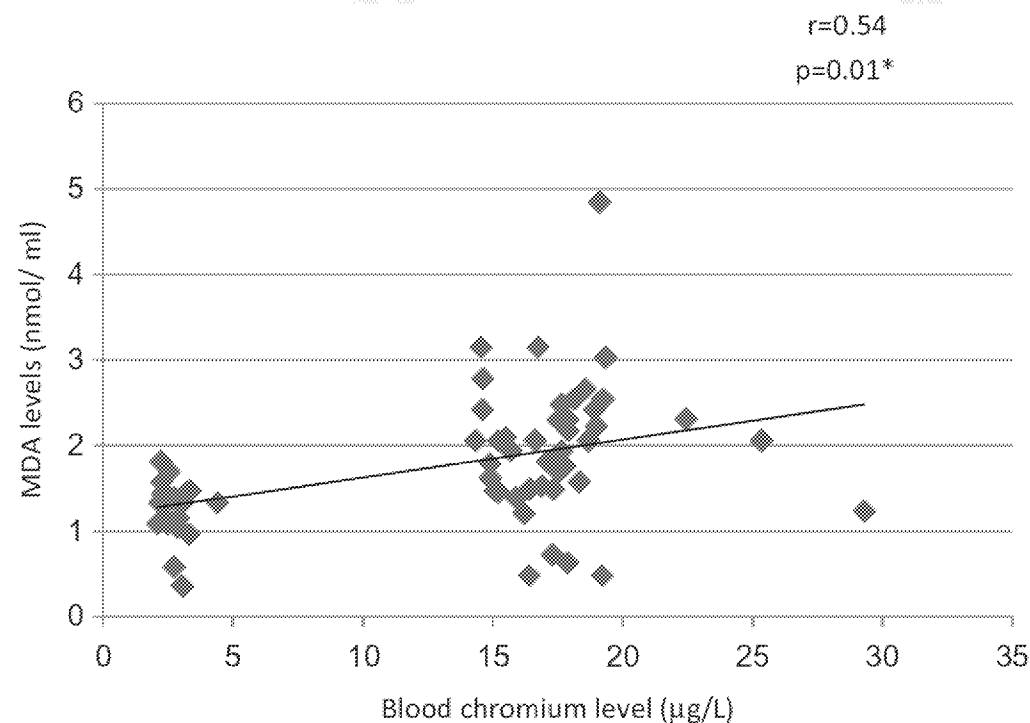
Elhosary et al. 2014. Inhalation Toxicology

How Many Experts Does it Take to Assess the Quality of an Exposure Measurement?

Potentially relevant areas of expertise:

- Analytical chemistry
- Human biomarkers
- Industrial hygiene
- Fieldwork experience
- Medicine, biology, disease etiology
- Epidemiology
- Toxicology
- Chemistry
- Chemical-specific knowledge
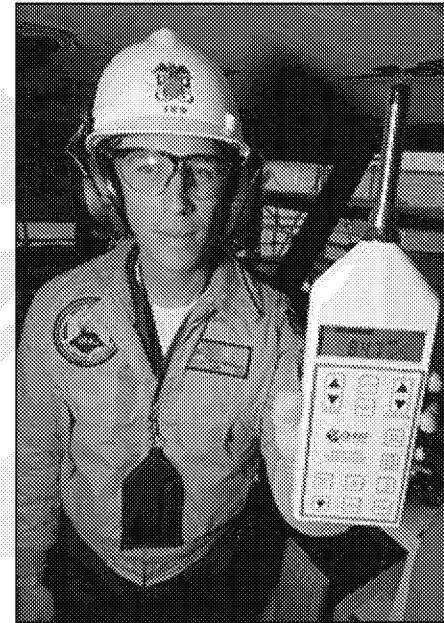
Considerations for Hexavalent Chromium (Cr[VI]) Exposure Measurements in Epidemiology Studies (1 of 2)

- Chemistry
  - Two oxidation states common in occupational environments: Cr(VI) or Cr(III) and *both may be present simultaneously*

- Analytical Chemistry
  - Reliable methods for Cr(VI) in air, or Total Cr in air, urine or blood.

- Toxicokinetics
  - Cr(VI) undergoes rapid reduction to Cr(III) in body

Considerations for Hexavalent Chromium (Cr[VI]) Exposure Measurements in Epidemiology Studies

- Disease Etiology
  - Relevant window (<u>timing</u>) of exposure
- Sampling protocols (air measurements)
  - PVC vs. cellulose fiber filter
  - <u>Time between</u> sample collection and analysis; <u>partial or full shift</u> sampling
- Industrial Hygiene Considerations
  - Electroplating: automated dipping vs. manual
  - Welding: Welding type; <u>duration</u> of task
  - Stainless steel and chromate production: (next slide)

Chromate Production Process
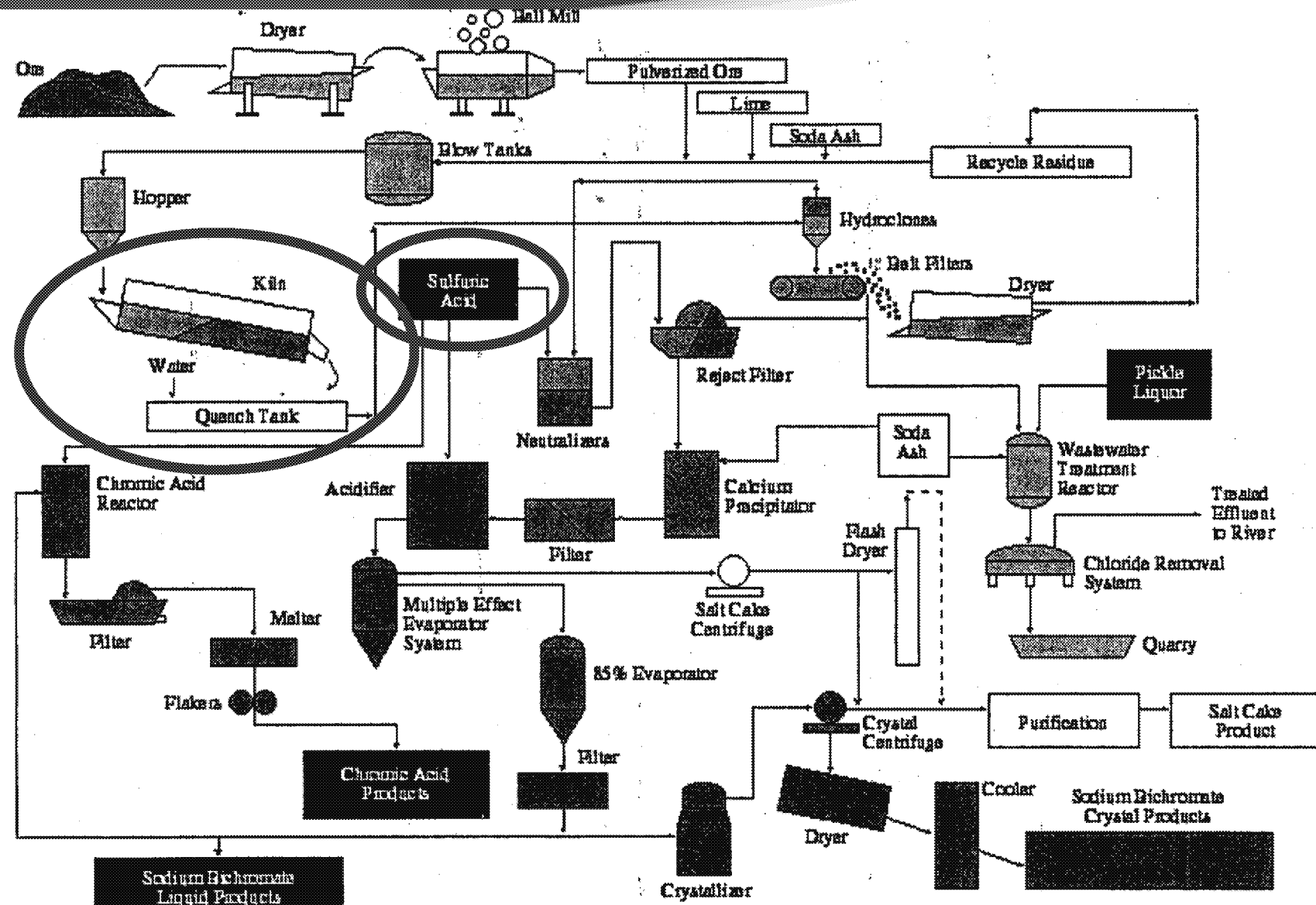
Source: Shaw Production, Inc. 2006. (OSHA rule docket)

Assessing Exposure Misclassification in Study of Danish Stainless Steel Welders

Paper 1 of 2 (Bonde et al. 1990) Exposed vs. Referents

Table 4 Exposure classification of participants in semen study

Exposure category	Welding method		No of subjects
Mild steel welders*			46
Low exposed	MMA, MAG, or both	31	
High exposed†	MMA	15	
Stainless steel welders	TIG		35
Referents‡			54
Electricians		22	
Drillers		16	
Machinists		9	
Unskilled		7	
Total			135

Paper 1 of 2 (Bonde et al. 1990)

Table 2   Total fume and metal concentrations in workroom air collected with personal samplers by random selected mild steel and stainless steel tungsten inert gas welders

| | Mild steel welders | | Stainless steel‡ welders | |
| | High exposed* | Low exposed† | | |
	Mean (SD)	Mean (SD)	Mean (SD)	p Value‖
Welding intermittence (%)	21·6 (5·0)	18·0 (9·6)	14·5 (8·8)	0·36
Total fumes (mg/m³)	4·7 (2·7)	3·2 (1·0)	1·3 (0·8)	0·05
Iron (mg/m³)	0·9 (0·3)	1·0 (0·5)	0·08 (0·06)	0·99
Manganese (µg/m³)	132·1 (102·6)	64·8 (49·9)	4·0 (2·1)	0·03
Copper (µg/m³)	7·3 (1·7)	14·9 (10·4)	5·5 (3·3)	0·06
Chromium total (µg/m³)	3·0 (1·8)	4·1 (9·0)	14·8 (11·4)	0·09
Chromium VI (µg/m³)	2·0 (1·2)	1·2 (1·2)	3·6 (2·8)	0·69

Bonde et al. 1990.

Paper 2 of 2 (Bonde and Ernst 1992)

	Concentration of post-shift urine chromium nmol mmol^{-1} creatinine		
	<1.07 n = 60	*1.07–1.78* n = 24	*>1.78* n = 23
Stainless steel welders, %	16	26	58
Mild steel welders, %	46	29	25
Non-welding metal workers, %	48	35	17
Electricians, %	100	0	0

Bonde and Ernst. 1992.

Study Results: Stainless Steel vs. Referents

Table 7 Semen parameters and sex hormones in mild steel welders, stainless steel welders, and referents

Parameter	Mild steel welders (n = 46)		Stainless steel welders (n = 35)		Referents (n = 54)		p Value*	p Value†
Sperm count per ejaculate (millions):								
Mean (SD)	153	(85)	138	(63)	184	(114)	NS	<0·05
Adjusted mean (SD)‡§	148	(85)	135	(58)	190	(113)	<0·05	<0·05
Semen volume (ml):								
Mean (SD)	2·8	(1·6)	2·4	(1·1)	3·1	(1·3)	NS	<0·05
Adjusted mean (SD)‡§	2·8	(1·6)	2·6	(1·1)	3·3	(1·4)	NS	<0·05
Sperm concentration (millions):								
Mean (SD)	57·9	(24·8)	58·4	(16·7)	58·6	(23·9)	NS	NS
Adjusted mean (SD)	56·1	(24·0)	56·4	(15·3)	55·1	(24·3)	NS	NS
Sperm concentration <20 million (% of subjects)‖	6·5		2·9		5·6		NS	NS
Normal morphology (%; mean (SD))	59·4	(18·5)	65·8	(15·7)	66·7	(17·1)	<0·01	NS
<50% normal forms ‖ (% of subjects)	21·7		14·3		14·8		NS	NS
Immature sperm forms ‖ (% of subjects)	8·7		17·1		3·7		NS	<0·05
Motile sperm (% of subjects) mean (SD)	54·8	(11·8)	51·0	(15·7)	57·7	(14·8))	NS	<0·05
<50% motile sperms‖ (% of subjects)	39·1		31·4		22·2		NS	NS
None or poor motility‖ (% of subjects)	45·7		51·4		22·2		<0·05	<0·01
Linear penetration (cm/hour; mean (SD))	3·5	(0·7)	3·8	(0·7)	3·8	(0·5)	<0·05	NS
Testosterone (nmol/l; mean (SD))	18·6	(6·4)	17·3	(5·8)	21·2	(8·0)*	NS	<0·05
FSH (IU/l; mean (SD))	5·7	(3·5)	4·4	(5·1)	4·9	(2·8)	NS	NS
LH (IU/l; mean (SD))	7·1	(2·9)	6·1	(2·4)	7·2	(2·7)	NS	NS

Bonde et al. 1990.

Study Results: 3 Exposure Groups (Low, Med, High)

Table 2 Sexual hormones and sperm parameters in metalworkers classified according to concentration of chromium in post-shift urine.

	Concentration of chromium nmol mmol^{-1} creatinine			Beta	P-value
	<1.07	1.07–1.78	>1.78		
Semen volume (ml), mean (1 s.d.)	2.9 (1.3)	3.0 (1.6)	3.2 (1.4)	+0.2	NS
Sperm concentration (million ml^{-1}), mean (1 s.d.)	54.5 (26.9)	62.8 (21.7)	50.7 (20.9)	−1.5	NS
Total sperm count (millions per ejaculation), mean (1 s.d.)	156.2 (100.9)	179.5 (103.1)	150.7 (90.7)	−0.8	NS
Proportion of normal sperm forms, %	65.8 (17.8)	61.0 (17.1)	56.8 (20.5)	−1.6	NS
Proportion of motile sperm, %	55.2 (14.6)	54.8 (11.9)	51.6 (16.4)	−0.5	NS
Sperm penetration rate (cm h^{-1}), mean (1 s.d.)	3.75 (0.56)	3.61 (0.68)	3.69 (0.79)	0.0	NS
Testosterone (nmol l^{-1}, mean (1 s.d.)	21.0 (7.8)	18.7 (7.3)	16.4 (5.6)	−1.2	NS
Follicle stimulating hormone (IU l^{-1}), mean (1 s.d.)	4.7 (2.9)	5.0 (2.6)	4.5 (2.2)	−0.1	NS
Luteinizing hormone (IU l^{-1}), mean (1 s.d.)	6.8 (3.0)	6.8 (2.4)	6.7 (2.8)	−0.1	NS

Beta is the regression coefficient (unadjusted).

Bonde and Ernst. 1992.

Exposure Sciences Expertise:
Where Can Epidemiologists Find It?

- In-house expertise (EPA regional offices, NERL)

- Other regulatory offices: Federal agencies, states, WHO, Health Canada, CDC/ATSDR, DoD

- Peer-reviewed literature

- Published laboratory protocols (e.g., NIOSH, CDC, EPA)

- Hire experts as contractors

- Dial-an-expert

Exposure Sciences, Epidemiology, & Protecting Human Health

- Measurements
  - Frequency, duration, magnitude of exposure
  - Health outcomes
- Estimated dose-response relationships
  - Approximation of underlying truth
  - Inform decisions that protect human health
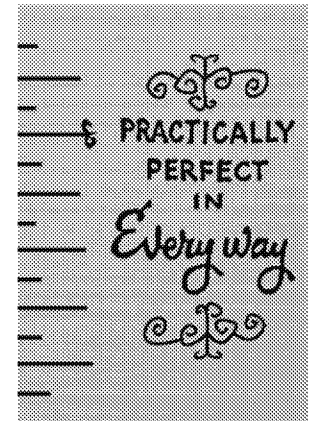
Questions?
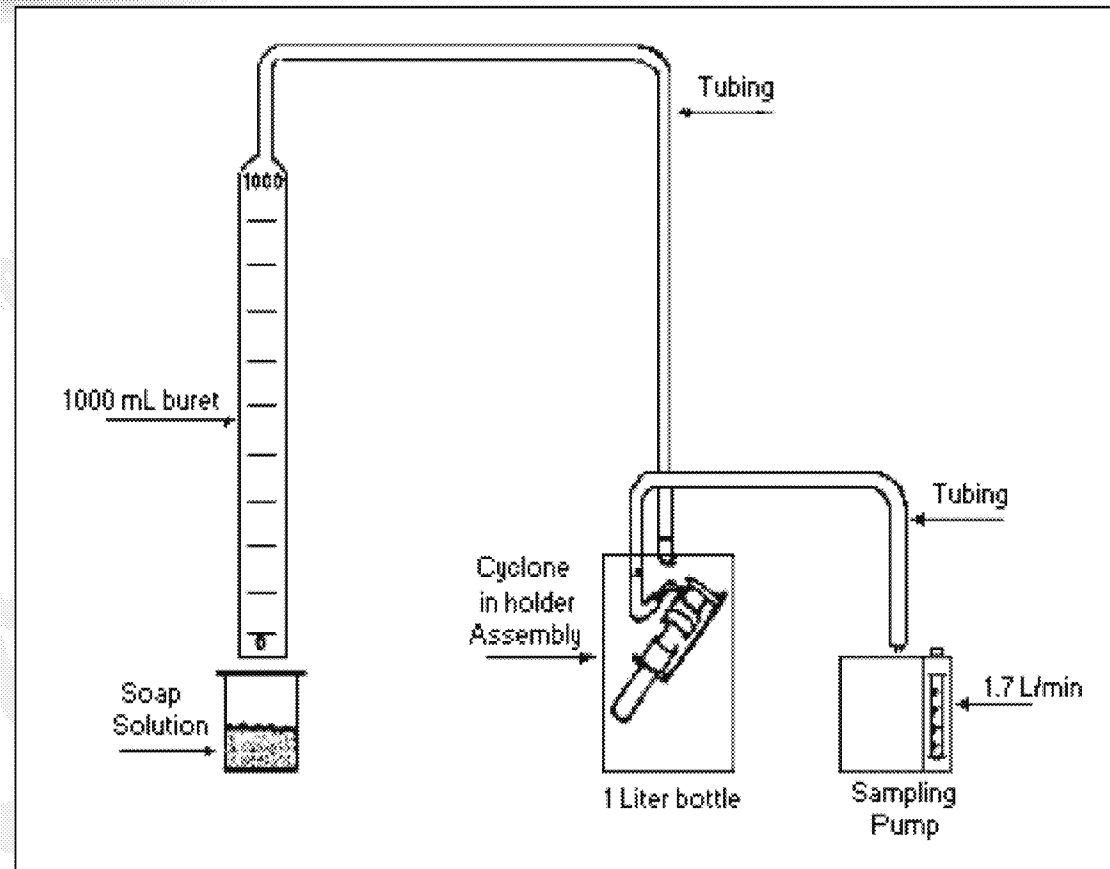
Fig. Soap bubble air pump calibration.
Source: OSHA Technical Manual. Personal Sampling for Air Contaminants.
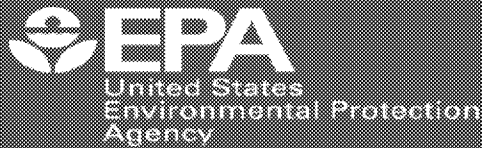
Application of Systematic Review in TSCA Risk Evaluations

April 25, 2019

Cathy Fehrenbacher, Acting Director
Risk Assessment Division

Eva Wong, Associate Branch Chief
Risk Assessment Division

Office of Chemical Safety and Pollution Prevention
Office of Pollution Prevention and Toxics (OPPT), Risk Assessment Division (RAD)

Outline

- Background on TSCA implementation, science standards and systematic review

- Key features of systematic review

  - Overview of systematic review process

  - Evaluation strategies to assess data/information quality

- Key takeaways

TSCA Background – A Timeline

- June 22, 2016 - The Frank R. Lautenberg Chemical Safety for the 21st Century Act updated the 1976 Toxic Substances Control Act

- December 19, 2016 - EPA issued Federal Register notice on our intent to conduct risk evaluations for the first 10 chemicals under the amended TSCA

- June 22, 2017- EPA released the scoping and supplemental documents for the 1st 10 risk evaluations, finalized new rules, and provided a guidance document for external parties

- May 2018 – Publication of TSCA Problem Formulation documents for the 1st 10 risk evaluations and Application of Systematic Review in TSCA Risk Evaluations

- **December 2019, with an optional 6 month extension** - EPA will publish final risk evaluations for 1st 10 chemicals

139

TSCA Science Requirements

TSCA
Systematic
Review
Process
(Figure 3-1, page 15, Application of
Systematic
Review in TSCA Risk Evaluations)

- ## BEST AVAILABLE SCIENCE (BAS)

  – Science that is reliable and unbiased

- ## WEIGHT OF THE SCIENTIFIC EVIDENCE (WoE)

  – Identifies and evaluates each stream of evidence

  – Integrates evidence as necessary and appropriate based upon strengths, limitations and relevance

  BAS AND WOE definitions can be found at 40 CFR 702.33

140

Systematic Review

- As defined by the Institute of Medicine, systematic review "is a scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies" (National Academy of Sciences, 2017).

- The goal of systematic review methods is to ensure that the review is **complete**, **unbiased**, **reproducible**, and **transparent** (Bilotta et al., 2014).

Application of Systematic Review for Existing Chemical Risk Evaluations Under TSCA

United States Environmental Protection Agency

Scoping/Problem formulation Phase		Analysis Phase		
1. Protocol Development →	2. Data Collection →	3. Data Evaluation →	4. Data Integration →	5. Summary of Findings (Exposure & Hazard Assessments) → Risk Characterization

TSCA Risk Evaluation
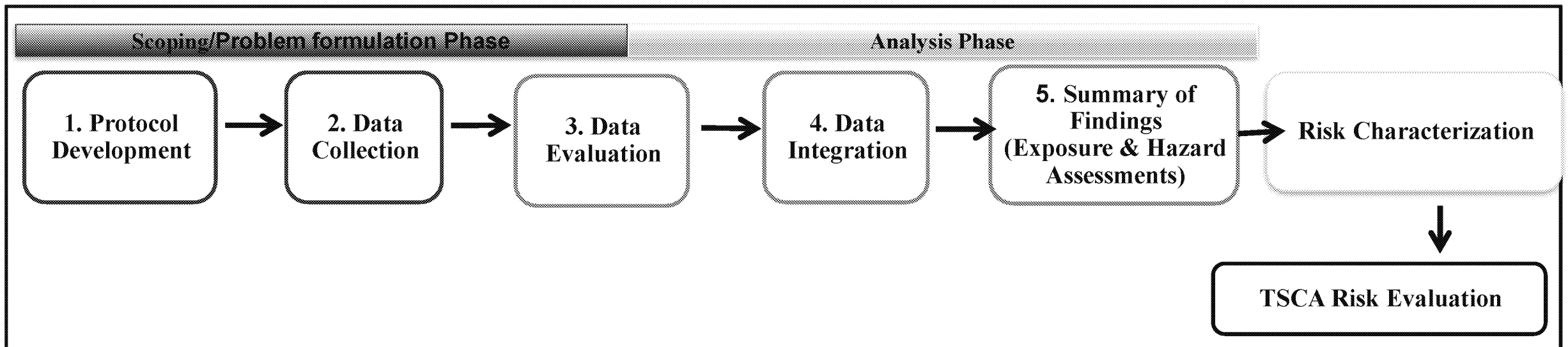
- EPA is required to meet the scientific standards in TSCA for best available science, utilizing a weight of the scientific evidence approach when conducting risk evaluations.

EPA
United States
Environmental Protection
Agency

Page 93 of

Application
of Systematic
Review in
TSCA Risk
Evaluations

Table E-1. Types of Exposure Data Sources

Type of Data Source	Definition
Monitoring Data	Measured chemical concentration(s) obtained from sampling of environmental media (e.g., air, water, soil, and biota) to observe and study conditions of the environment. Monitoring data also include measured concentrations of chemicals or their metabolites in biological matrices (i.e., blood, urine, breastmilk, breath, hair, and organs) that provide direct evidence about exposure of environmental contaminants in humans and wildlife, as well as measured chemical concentrations obtained from personal exposure monitoring (i.e., breathing zone, skin patch samples).
Modeling Data	Calculated values derived from computational models for estimation of environmental concentrations (i.e., indoor, outdoor, microenvironments) and uptakes (e.g., ADD, LADD, Cmax, or AUC) associated with relevant exposure scenarios and routes (i.e., inhalation, oral, dermal).
Survey-based Data	Data collected from survey questionnaires about activity and use patterns (e.g., habits, practices, food intake) to evaluate exposure to an individual, a population segment or a population.
Epidemiological Data	Exposure data obtained from epidemiological studies collected as part of the examination of the association between chemical exposure and the occurrence and causes of health effects in human populations. The data may also come from case study reports which characterize exposures to one person.
Experimental Data	Data obtained from experimental studies conducted in a controlled environment with pre-defined testing conditions. Examples include data from laboratory/chamber tests such as those conducted for product testing, source characterization, emissions testing, and migration testing. Experimental data may also include chemical concentrations from personal exposure or biomonitoring studies conducted in laboratory/chamber test settings.
Completed Exposure Assessments and Risk Characterizations	Data reported in completed exposure assessments and risk characterizations containing a broad range of exposure data types (e.g., media concentrations, doses, estimated values, exposure factors). Examples: ATSDR assessments, risk assessments completed by other countries.
Database Sources Not Unique to a Chemical	Data obtained from large databases which collate information for a wide variety of chemicals using methods that are reasonable and consistent with sound scientific theory and/or accepted approaches, and are from sources generally using sound methods and/or approaches (e.g., state or federal governments, academia). Example databases: NHANES, STORET.

143

Evaluation Strategies to Assess Data/Information Quality

- Structured framework with numerical scoring to categorize quality of data/information sources

- Developed pre-defined criteria for the following data/information streams:

  - Data Quality Criteria for exposure to general population, consumers and environmental exposures (Appendix E) with evaluation criteria for the following types of data, including those with serious flaws:

    - *Monitoring Data, page 99 – 107*
    - *Modeling Data, pages 108 – 112*
    - *Survey Data, pages 113 – 118*
    - *Epidemiology Data, pages 119 – 129*
    - *Experimental Data, pages 130-137*
    - *Database Data, pages 138 – 142*
    - *Completed Exposure Assessments and Risk Characterizations, pages 143 - 145*

144

E.6.3   Survey Data

Table E-10. Serious Flaws that Would Make Sources of Survey Data Unacceptable for Use in the Exposure Assessment

Optimization of the list of serious flaws may occur after pilot calibration exercises.

Domain	Metric	Description of Serious Flaw(s) in Data Source
Reliability	Data Collection Methodology	Data collection methods are not described.
		Data collection methods used are not appropriate (i.e., scientifically sound) for the target population, the intended purpose, data requirements of the survey, or the target response rate.
		There are numerous inconsistencies in the reporting of data collection information resulting in high uncertainty in the data collection methods used.
	Data Analysis Methodology	Data analysis methodology is not described.
		Data analysis methodology is not appropriate (i.e., scientifically sound) for the intended purpose of the survey and the data/information collected.
		There are numerous inconsistencies in the reporting of analytical information resulting in high uncertainty in the data analysis methods used.
Representative	Geographic Area	Geographic location is not reported, discussed, or referenced.
	Sampling/ Sampling Size	Sampling procedures (e.g., stratified sampling, cluster sampling, multi-stage sampling, non-probability sampling, etc.) are not documented in the data source or companion source.
		Sample size is not reported.
	Response Rate	This metric does not have an unacceptable criterion..
Accessibility / Clarity	Reporting of Results	There are numerous inconsistencies or errors in the calculation and/or reporting of results, resulting in highly uncertain reported results.
	Quality Assurance	QA/QC issues have been identified which significantly interfere with the overall reliability of the survey results.
Variability and Uncertainty	Variability and Uncertainty	Estimates are highly uncertain based on characterization of variability and uncertainty.

Note:
QA/QC = Quality assurance/quality control

Table E-4.Scoring Example for Monitoring Data

Page 97 of

Application of
Systematic
Review in
TSCA Risk
Evaluations

Metric	Selected Metric Score	Metric Weighting Factor	Weighted Metric Score
Metric 1: Sampling Methodology	1	1	1
Metric 2: Analytical Methodology	2	1	2
Metric 3: Selection of Biomarker of Exposure	2	1	2
Metric 4: Geographic Area	1	1	1
Metric 5: Temporality	1	1	1
Metric 6: Spatial and Temporal Variability	1	1	1
Metric 7: Exposure Scenario	3	1	3
Metric 8: Reporting of Results	1	1	1
Metric 9: Quality Assurance	2	1	2
Metric 10: Variability and Uncertainty	2	1	2
		Sum = 10	Sum = 16
∑(Metric Score × Metric Weighting Factor)/∑(Metric Weighting Factors)			=16/10=1.6

146

Overall Score: 1.6

(High)

Data Integration:
Planning, Execution and Assessment Phase

Refer to page 18 of document

Data Integration Using the Weight of the Scientific Evidence	
Planning Phase	• Develop and document strategy for analyzing and summarizing data/information across studies within each evidence stream, including strengths, limitations and relevance of the study. • Develop and document strategy for weighing and integrating evidence across evidence streams, including strengths, limitations and relevance of the study.
Execution Phase	• Conduct and document the analysis and synthesis of the evidence. • Document the conclusions within each evidence stream. • Weigh, integrate and document results across sets of studies within and across evidence streams. • Document any professional judgment, including underlying assumptions that are used to support the risk evaluation.
Assessment phase (QA/QC)	• Specify process for assuring quality of the data being analyzed, synthesized and integrated. • Specify process for comparing results and resolving differences between reviewers.

Further details on evidence integration will be provided along with the publication of the draft TSCA risk evaluations.

147

Key Takeaways

- Exposure information can be obtained from studies and other sources of information

- Systematic review process and evaluation strategies were developed to meet TSCA science standards

- Goal is to produce transparent, consistent and scientifically robust risk evaluations

- Data evaluation criteria can also be useful in developing protocols for collecting information and data

148

Using SR Tools in Development of the ISA Exposure Assessment Review

Systematic Review in Exposure Science Summit / EPA Potomac Yard South

Jeanette M. Reyes[1] and Jennifer Richmond-Bryant[2]
[1]ORISE Research Participation Program, hosted at USEPA, RTP, NC
[2]Office of Research and Development, NCEA, USEPA, RTP, NC

Office of Research and Development
National Center for Environmental Assessment-RTP, Environmental Media Assessment Group

Thursday, April 25, 2019

Integrated Science Assessment (ISA)

- **Clean Air Act (CAA)**
  - "…Clean Air Act (CAA) govern the establishment, review, and revision, as appropriate, of the National Ambient Air Quality Standards (NAAQS)…"
  - Criteria air pollutants: PM, O_3, Pb, NO_X, SO_X, CO
- **ISA Overview**
  - "The ISA provides a concise review, synthesis, and evaluation of the most policy-relevant science to serve as a scientific foundation for the review of the… NAAQS." (U.S. EPA, 2013)
  - Human health and welfare
  - Evaluates evidence from multiple disciplines including: atmospheric chemistry, exposure assessment, epidemiology, toxicology, ecology, and climate
  - 1) Evaluation of literature published since the last ISA and 2) presentation of causal determinations based on application of structured, weight of evidence framework
  - ISA → REA → PA → NAAQS

Time

Planning: based on new scientific information, policy-relevant issues, standardized charge questions
Call for information, Workshop (if warranted), **Planning Documents**

↓

Assessment: of policy implications of current scientific information, particularly with regard to standard (indicator, averaging time, form, level)
Scientific Assessment, Risk/Exposure Assessment, Policy Assessment

↓

Rulemaking: Agency decision making, interagency review and public comments process

Public Comments

Clean Air Scientific Advisory Committee (CASAC) review

Implementation Considerations and 109 (d)(2)(C)(iv) Assessment

Public Comments

(Pruitt, 2018)

ISA Exposure Appendix

- Exposure connects **atmospheric chemistry** to **epidemiology**
- Components of exposure appendix
  - Measurements, modeling
  - Application of exposure assessment in epidemiology studies
  - Exposure error influence on epidemiologic study results
- Table 3-2 (SO_X ISA, 2017)
  - Exposure method descriptions with implications for error and exposure assignment in epidemiologic studies

Exposure Concentration Assignment Method	Description	Epidemiologic Application	Strengths	Limitations	Exposure Errors
Dispersion modeling (Section 3.3.2.4).	Ambient SO_2 concentrations at specific locations are estimated from emissions, meteorology, and atmospheric physics.	Long-term epidemiologic studies: surrogate for ambient SO_2 exposure concentration within a city or geographic region.	High spatial and temporal resolution, accounts for atmospheric physics from local emission sources	Resource intensive, very limited representation of atmospheric chemistry or background SO_2 concentrations.	Potential for bias where the dispersion model does not capture boundary conditions and resulting fluid dynamics well (e.g., in large cities with urban topography affecting dispersion).
Chemical transport model (Section 3.3.2.5).	Grid-based ambient SO_2 concentrations are estimated from emissions, meteorology, and atmospheric chemistry and physics.	Long-term epidemiologic studies: surrogate for ambient SO_2 exposure concentration, sometimes within a city but more typically across a larger region.	Strengths include accounting for stack parameters, emission rates, mixing height, atmospheric stability, meteorology, atmospheric chemistry, and complex terrain.	Limited grid cell resolution (i.e., grid cell length scale is typically 4–36 km and much larger than plume width), resource-intensive, spatial smoothing of local SO_2 emissions sources.	Potential for bias if grid cells are too large to capture spatial variability of ambient SO_2 exposures.
Microenvironmental model (e.g., APEX, SHEDS) (Section 3.3.2.6).	Estimates distributions of micro-environmental SO_2 concentrations, exposures, and doses for populations (e.g., census tracts) based on air quality data, demographic variables, and activity patterns.	Panel epidemiologic studies; no epidemiologic studies cited here use micro-environmental models.	Accounts for variability of SO_2 exposures across large populations, accounts for different concentrations in different microenvironments, accounts for location-activity information.	Models simulate individuals and their exposures, but they do not represent an actual population.	Potential for bias when the modeled distributions of ambient SO_2 concentration, indoor:outdoor pollutant ratios, and time-activity patterns differ from the true distributions.

APEX = Air Pollutants Exposure model; FEM = Federal Equivalent Method; FRM = Federal Reference Method; IDW = inverse distance weighting; SHEDS = Stochastic Human Exposure and Dose Simulation; SO_2 = sulfur dioxide.

(U.S. EPA, 2017)

Systematic Review (SR) Practices for Exposure Assessment Chapter in Previous ISAs

Broad literature search within a given time window	→	Automatic topic classification: "Exposure"	→	Topic searches in text

Title reads for considered references	→	Full text reads for scoping considerations	→	References within the ISA

152
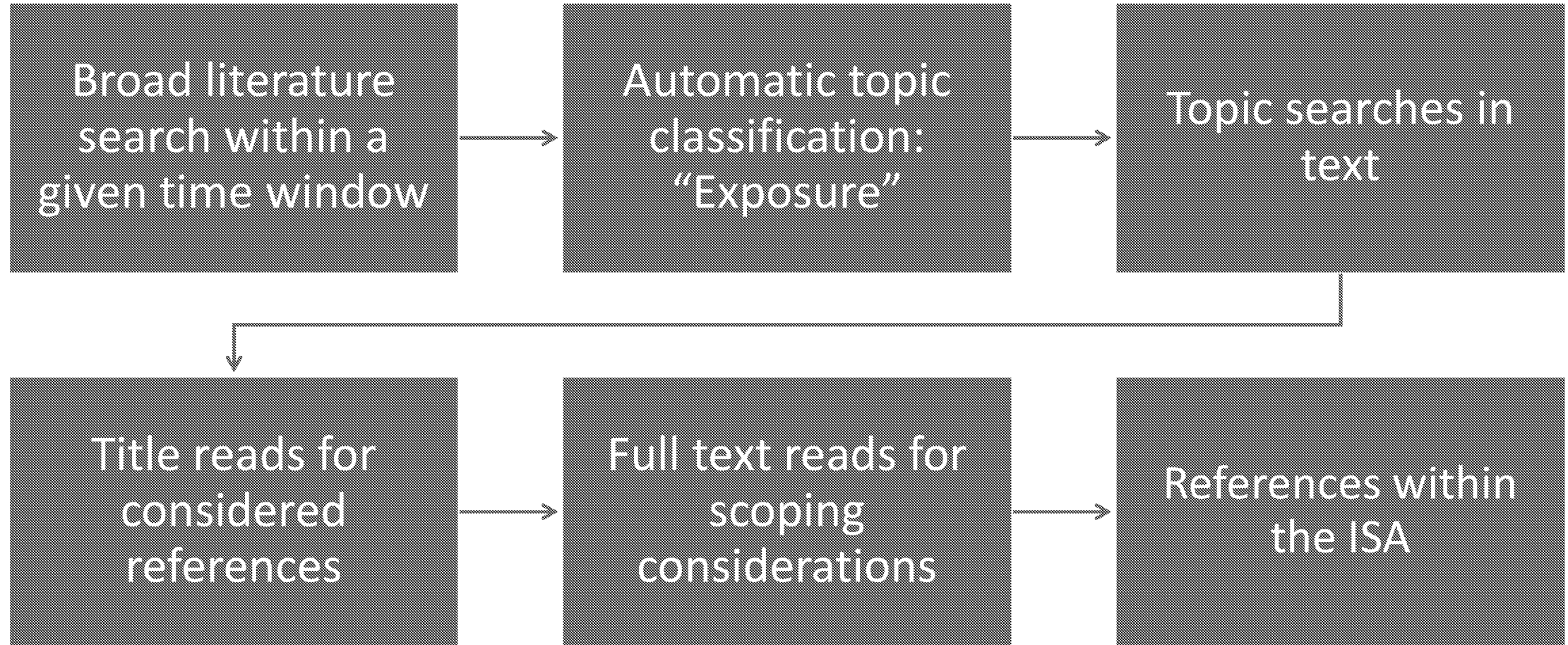
Adapting SR Tools for the Timeline of the Upcoming Ozone ISA

- Timeline: "Back-to-Basics Memo" (May 2018)
  - "I am directing Agency staff to begin the next review of the ozone NAAQS so EPA will be ready to finalize any necessary revisions by the statutorily required five-year deadline (October 2020)." (Pruitt, 2018)
- Considerations in applying SR tools to the ISA
  - The ISA asks broad questions about a variety of health and ecological endpoints
  - Covers six disciplines
  - 30,000+ references (for ozone keyword search)
  - The ISA applies a weight of evidence framework
- Innovative use of SR tools in the current ISA
  - Increase efficiency and transparency
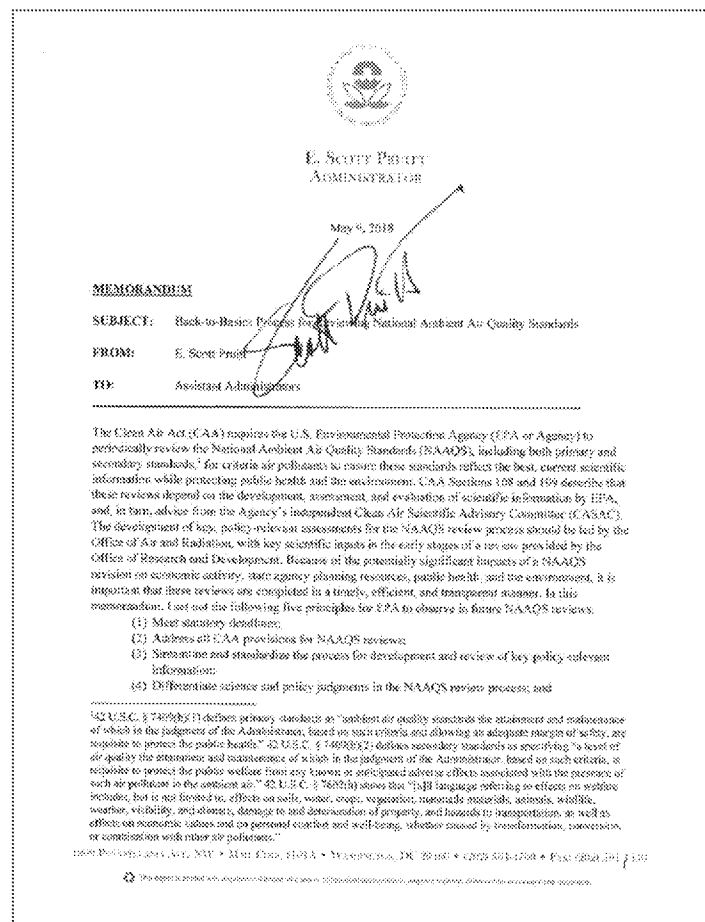
(Pruitt, 2018)

Literature Screening Process

- HERO (Health and Environmental Research Online)
  - "...HERO is a database of scientific studies and other references used to develop EPA's risk assessments aimed at understanding the health and environmental effects of pollutants and chemicals." (https://hero.epa.gov/hero/index.cfm/content/basic)
  - Databases: PubMed, TOXLINE, and Web of Science (U.S. EPA, 2018)
  - Search for "ozone OR O3", between January 1, 2011 and March 30, 2018 (U.S. EPA, 2018)
  - Number of references: **30,797**

- Automatic topic classification: seed for "Exposure" references
  - 506 studies (2013 Ozone ISA: 222, 2016 NO_X ISA: 340, 2017 SO_X ISA: 282)
  - Number of studies: **5,135**

Literature Search

Screened

Considered

Title/abstract

yes

no

Full Text

PECOS

Included

yes

no

Citations from past assessments

Peer recommendations
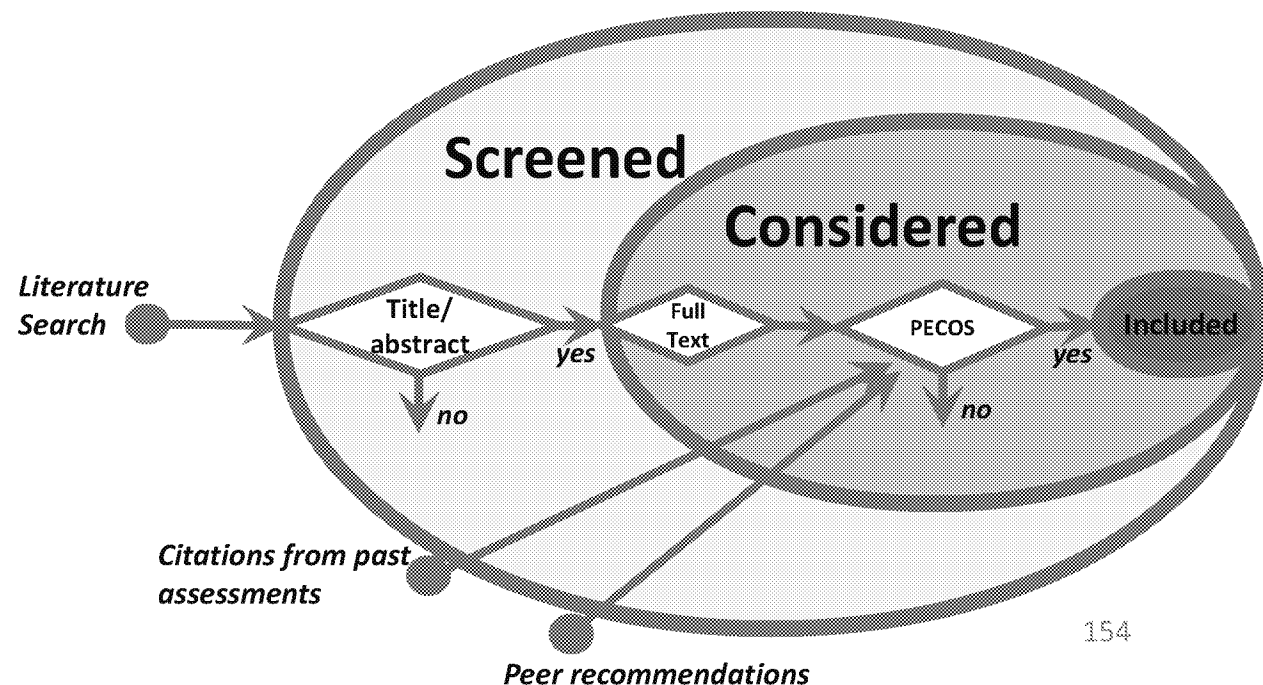
SWIFT-AS

- SWIFT-AS (Sciome Workbench for Interactive computer-Facilitated Text-mining-Active Screener)
  - Title and abstract screening
  - Machine Learning
  - Optional screening questions (i.e., appendix-specific "tagging")
  - Number of references screened: **3,093**
  - Number of references for inclusion: **1,824**
  - 95% recall comparable to manual screening

Legend:
- Your Predicted Recall
- Predicted Normal Screening
- 95% Inclusion

X-axis: Number of "Exposure" References (0, 1k, 2k, 3k, 4k, 5k)

Y-axis: Percentage of Included Documents (0, 25, 50, 75, 100)
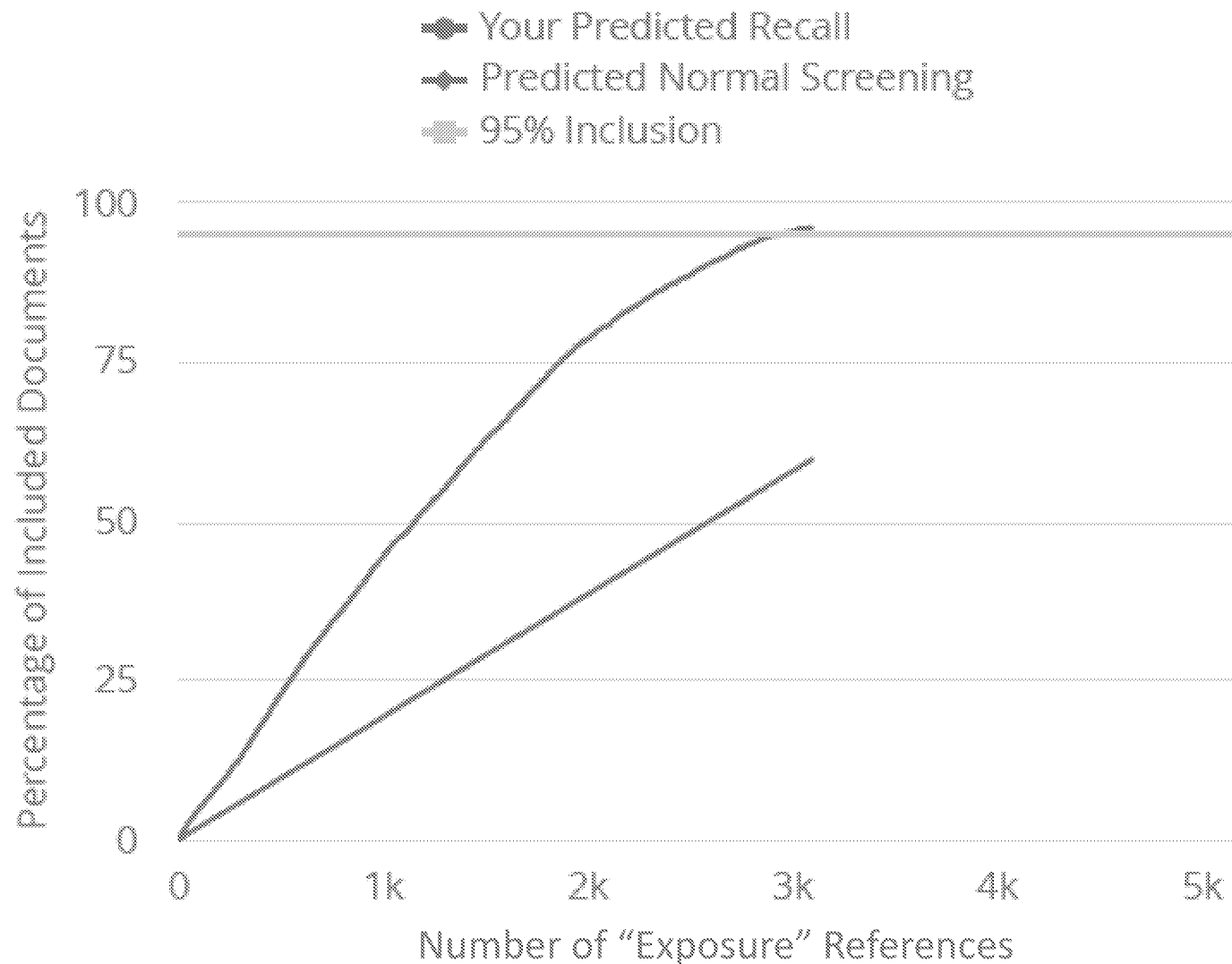
SWIFT-AS Screen Shot

Updating screening completed by Richmond-bryant,Jennife

Screen Reference

You have reached the predicted inclusion threshold and can stop screening.

Currently Screening: Level 1 - Title & Abstract

Inclusion Color
Exclusion Color

...ly monitoring data in Chicago

EMAG staff designate whether to include based on review of title and abstract

- Yes, consider this reference
- No, exclude the reference

Quality System monitoring network provides surface measurements of concentrations at hourly resolution over multiple years, revealing variations at the annual, seasonal, day of week and ...used to estimate the temporal profiles ...gy, ozone concentrations, and ...005 to 2016 available at 6 sites in ...ver the length of the time series. The ...areas, with 32% reductions on ...more residential areas with 20% ...weekday diurnal profiles follow a ...afternoon rush hours, but only a ...6 sites suggest that there are ...ofiles on Saturday have less variation ...ndays are very different from each ...arly evening. The results suggest that ...e speed and congestion must be taken ...ons and the weekend effect.

Include/Exclude Question

Consider this reference? *
- Yes, consider this reference
- No, exclude the reference

Main

Study type? (Select all that apply)
- [ ] Population monitoring
- [ ] Personal monitoring
- [x] Modeling
- [ ] Satellite/hybrid
- [ ] Exposure relationships
- [ ] Time activity
- [x] Spatial variability
- [ ] Averting behavior
- [ ] Instrument error
- [ ] Other

- Population monitoring
- Personal monitoring
- Modeling
- Satellite/hybrid
- Exposure relationships
- Time activity
- Spatial variability
- Averting behavior
- Instrument error
- Other

Options to categorize study type facilitate easy incorporation of studies into outline

The reference is currently included

Display Instructions

156

Exposure PECOS Statement

- **Uncertainty Tier Description**

Tier 1	Exposure assessment methods are well validated with low spatial and/or temporal error
Tier 2	Exposure assessment methods are either well validated or provide low spatial and/or temporal error in U.S. or Canadian studies
Tier 3	Exposure assessment methods are neither well validated nor provide low spatial and/or temporal error in U.S., Canadian, western European, or Australian studies

-

Uncertainty Tier	Epidemiologic Study Design	PECOS
Tier 1: Exposure assessment methods are well validated with low spatial and/or temporal error	Short-term	In a domain containing any U.S. or Canadian population, including populations or life stages that might be at increased risk **(P)**, how are exposure assessment methods of different designs used to represent **(C)** true (but uncharacterized) exposure to ozone **(E)** evaluated with respect to validation and temporal error **(O)** for application in a short-term exposure study **(S)**?

PECOS: Population, Exposure, Comparator, Outcome, Study design

Additional Text Screening

- After SWIFT-AS
  - Number of studies: 646 (US), 105 (Canada)
  - Title/abstract screening for further methods-specific scoping
  - Number of studies after additional full text screening in EndNote: **332**

Methods	Search Terms	#
Fixed-site monitoring	[Any field contains federal reference method] OR [Any field contains federal equivalence method] OR [Any field contains fixed site monitor] OR [Any field contains central site monitor] OR [Any field contains ambient monitor]	12

Methods	
Fixed-site monitoring	12
Microenvironmental monitors	0
Active personal monitors, Passive personal monitors	8
Data averaging	10
Inverse distance weighting	2
Kriging	18
Land use regression	8
Spatiotemporal modeling	19
Chemical transport modeling	176
Hybrid approaches	40
Microenvironmental modeling	6
Satellite observations	74
Other	
Exposure relationships	49
Correlations (AQS data)	
Interpreting exposure error for use in epidemiology studies	19
Total (with duplicates)	**441**
Total (without duplicates)	**332**

Qualitative Assessment for Exposure Study Characteristics

- **Exposure assessment methods are clearly described.**
  - For **measurements**, this includes descriptions of the samplers, sampler location, sampling interval and duration, and other relevant details.
  - For **models**, this includes mathematical model developed or used to represent physics and/or chemistry, and (as relevant): choices of independent variables, grid cell size and distribution, and input data.

- **Selected exposure assessment methods make sense for the situation studied.**
  - Methods were selected with the **health effect data** in mind.
  - Methods selected are the **most appropriate** possible given the scenario being studied (see hierarchical list from Nieuwenhuijsen study) in terms of the **physics and/or chemistry** of the problem; the size of the **study domain** and the spatial and temporal **resolution** are chosen such that the probabilistic distribution of the exposure estimates is a good representation of the probabilistic distribution of the true exposures among the population studied.
  - If a model is transferred from one spatial domain or population to another, the model is **generalizable** enough that it provides a reasonable representation of the new spatial domain or population.

Qualitative Assessment for Exposure Study Characteristics (continued)

- **Assumptions of the methods are clearly stated.**
- **Uncertainties and limitations of the method are clearly stated, including but not limited to:**
  - Scenario represented by the model.
  - Simplifications made in the model.
  - Techniques used.
  - Availability and/or missingness of input data.
- **Quality assurance testing has been performed.**
  - All input data have undergone **quality assurance** testing.
  - **Cross-validation** of models is thorough (number and location of validation points represents the locations of study participants, duration and interval of sampling for cross-validation is representative of important time scales of the study so that the distribution of cross-validation data should match the distribution of true exposures).
  - Selected **statistical measures** of quality assurance are appropriate and clearly reported (both for the model evaluation procedure, such as number of validation locations, and model evaluation results, such as RMSE) are reported.

Evidence Inventories (EIs)

- EIs summarize the studies' features and the strengths and limitations of the methods

- Standardized extraction of study details and data into evidence inventories allowed for the **automation of table creation** for presentation of information in the ISA

In Summary: SR Practices for Exposure Assessment Chapter in the Upcoming Ozone ISA

HERO (PubMed, Web of Science, ToxNet) 2011-2018

→

Ozone Keyword Search
- 30,797 References

→

Automatic Topic Classification for "Exposure" (HERO)
- 5,135 References

→

SWIFT-AS: Title/Abstract Screening
- (1,269 Excluded)
- (2,042 not screened)
- 1,824 References

Geographic Scoping (only US and Canada studies)
- 646 US References
- 105 Canada References
- (Note: not mutually exclusive)

→

Additional Title/Abstract Keyword Screening (EndNote)
- 332 References

→

Full Text Screening: ISA Relevant
- US: 251 References
- Canada: 33 References

→

Full Text Screening: PECOS Relevant
- US: 137 References
- Canada: 16 References

Full Text Screening: Study Quality Documentation
- US: 126 References
- Canada: 16 References

→

Exposure references for inclusion in ISA: 142

New to ISA

- Acknowledgements
  - NCEA-RTP/EMAG management: Jennifer Nichols (NCEA-RTP/EMAG Acting Branch Chief), Steven Dutton (NCEA-RTP Deputy Director), and John Vandenberg (NCEA-RTP Division Director)
  - Ryan Jones (HERO) and Jennifer Nichols (SR Implementation)
  - Thomas Luben and Meredith Lassiter (Ozone Assessment Leads), Rebecca Daniels (Ozone Project Manager)

- Contact Information
  - Jeanette Reyes, PhD (reyes.jeanette@epa.gov)
  - Jennifer Richmond-Bryant, PhD (richmond-bryant.jennifer@epa.gov)

References

- Pruitt, ES (2018). Memo from E. Scott Pruitt, Administrator, U.S. EPA to Assistant Administrators. SUBJECT: Back-to-Basics Process for Reviewing National Ambient Air Quality Standards. May 9, 2018. Available: https://www.epa.gov/criteria-air-pollutants/back-basics-process-reviewing-national-ambient-air-quality-standards.

- U.S. EPA (U.S. Environmental Protection Agency). (2013). Integrated science assessment for ozone and related photochemical oxidants [EPA Report]. (EPA/600/R-10/076F). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment-RTP Division. http://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=247492

- U.S. EPA (U.S. Environmental Protection Agency). (2016). Integrated review plan for the national ambient air quality standards for particulate matter [EPA Report]. (EPA-452/R-16-005). Research Triangle Park, NC. https://yosemite.epa.gov/sab/sabproduct.nsf/0/eb862b233fbd0cde85257dda004fcb8c!OpenDocument&TableRow=2.0

- U.S. EPA (U.S. Environmental Protection Agency). (2017). Integrated science assessment for sulfur oxides – health criteria [EPA Report]. (EPA/600/R-17/451). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment-RTP Division. http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=533653

- U.S. EPA (U.S. Environmental Protection Agency). (2018). Integrated review plan for the ozone national ambient air quality standards (External Review Draft) [EPA Report]. Research Triangle Park, NC: U.S. Environmental Protection Agency, National Center for Environmental Assessment. https://yosemite.epa.gov/sab/sabproduct.nsf/264cb1227d55e02c85257402007446a4/E18E92A94AF87D6C852582BB004CDF75/$File/O3-IRP-draft-Oct2018-ForRelease-Oct31-2018.pdf

- Slide 2 Quote: https://www.epa.gov/criteria-air-pollutants/process-reviewing-national-ambient-air-quality-standards

EXTRA SLIDES

Additional Text Screening

Section	Search terms	#
Methods		
Fixed-site monitoring	[Any field contains federal reference method] OR [Any field contains federal equivalence method] OR [Any field contains fixed site monitor] OR [Any field contains central site monitor] OR [Any field contains ambient monitor]	12
Microenvironmental monitors	[Any field contains microenvironmental monitor] OR [Any field contains microenvironmental sampler]	0
Active personal monitors	[Any field contains personal monitor] OR [Any field contains personal sampler] OR [Any field contains wearable] OR [Any field contains	8
Passive personal monitors	passive sampler] OR [Any field contains passive monitor] OR [Any field contains active sampler] OR [Any field contains active monitor]	
Data averaging	[Any field contains averaging]	10
Inverse distance weighting	[Any field contains inverse distance]	2
Kriging	[Any field contains krig*] OR [Any field contains autocorrelat*]	18
Land use regression	[Any field contains land use regression]	8
Spatiotemporal modeling	[Any field contains spatiotemporal model*] OR [Any field contains space-time] OR [Any field contains spatial-temporal] OR [Any field contains geostatistic*]	19
Chemical transport modeling	[Any field contains CMAQ*] OR [Any field contains GEOS-Chem*] OR [Any field contains WRF*] OR [Any field contains chemical transport model*] OR [Any field contains CTM] OR [Any field contains CHIMERE*] OR [Any field contains CAMx*]	176
Hybrid approaches	WILL BE DERIVED FROM OTHER SEARCHES AND [Any field contains hybrid] OR [Any field contains fusion] OR [Any field contains assimilation] OR [downscal*] OR [down scal*]	40
Microenvironmental modeling	[Any field contains microenvironmental] OR [Any field contains APEX] OR [Any field contains SHEDS]	6
Satellite observations	[Any field contains satellite] OR [Any field contains remote sens*] OR [Any field contains AOD] OR [Any field contains TM5] OR [Any field contains MODIS] OR [Any field contains Terra]	74
Other		
Exposure relationships	[Any field contains infiltrat*] OR [Any field contains indoor] OR [Any field contains personal]	49
Correlations (AQS data)		
Interpreting exposure error for use in epidemiology studies	[Any field contains bias correction] OR [Any field contains exposure error] OR [Any field contains effect estimate]	19
Total (with duplicates)		**441**
Total (without duplicates)		**332**

Exposure PECOS Statement

Uncertainty Tier	Epidemiologic Study Design	Example PECOS
Tier 1: Exposure assessment methods are well validated with low spatial and/or temporal error	Short-term	In a domain containing any U.S. or Canadian population, including populations or life stages that might be at increased risk **(P)**, how are exposure assessment methods of different designs used to represent **(C)** true (but uncharacterized) exposure to ozone **(E)** evaluated with respect to validation and temporal error **(O)** for application in a short-term exposure study **(S)**?
	Long-term	In a domain containing any U.S. or Canadian population, including populations or life stages that might be at increased risk **(P)**, how are exposure assessment methods of different designs used to represent **(C)** true (but uncharacterized) exposure to ozone **(E)** evaluated with respect to validation and spatial error **(O)** for application in a long-term exposure study **(S)**?
Tier 2: Exposure assessment methods are either well validated or provide low spatial and/or temporal error in U.S. or Canadian studies	Short-term	In a domain containing any U.S., Canadian, western European, or Australian population, including populations or life stages that might be at increased risk **(P)**, how are exposure assessment methods of different designs used to represent **(C)** true (but uncharacterized) exposure to ozone **(E)** evaluated with respect to validation and temporal error **(O)** for application in a short-term exposure study **(S)**?
	Long-term	In a domain containing any U.S., Canadian, western European, or Australian population, including populations or life stages that might be at increased risk **(P)**, how are exposure assessment methods of different designs used to represent **(C)** true (but uncharacterized) exposure to ozone **(E)** evaluated with respect to validation and spatial error **(O)** for application in a long-term exposure study **(S)**?
Tier 3: Exposure assessment methods are neither well validated nor provide low spatial and/or temporal error in U.S., Canadian, western European, or Australian studies	Short-term	In a domain containing any population, including populations or life stages that might be at increased risk **(P)**, are exposure assessment methods of different designs used to represent **(C)** true (but uncharacterized) exposure to ozone **(E)** evaluated with respect to validation and temporal error **(O)** for application in a short-term exposure study **(S)**?
	Long-term	In a domain containing any population, including populations or life stages that might be at increased risk **(P)**, how are exposure assessment methods of different designs used to represent **(C)** true (but uncharacterized) exposure to ozone **(E)** evaluated with respect to validation and spatial error **(O)** for application in a long-term exposure study **(S)**?

Population: the general population, all age groups, whose exposure to ozone we want to represent within some spatial domain. Often, there is not a clear characterization of the exposed individuals, so it is necessary to make assumptions about who (what locations) should be included

Exposure: true short-term (hours to days) or long-term (months to years) ambient air ozone exposure (where $E = C{\times}t$); true exposure is unknown at both the individual and population levels but is estimated using exposure assessment methods

Comparator: the exposure assessment method

Outcome: evaluation of the exposure assessment method in comparison with reference measurements at validation sites

Study design: epidemiologic studies on health effects of ozone consisting of cross-sectional, case-control, case-crossover, cohort, panel and time-series studies

Future Directions for Improving Exposure Assessments in Air Pollution Epidemiology Studies

Michael Breen

US Environmental Protection Agency
Research Triangle Park, North Carolina, United States

Systematic Review in Exposure Science Summit,
April 2019

Disclaimer

The views expressed in this presentation are those of the authors and do not necessarily reflect the views or policies of the U.S. EPA

Science Question & Relevance

- **Science Question**
  - **Can individual-level exposure models integrated with wearable sensor technologies (e.g., GPS, accelerometers, smartphones):**
    - **Improve exposure assessments in risk estimates for epidemiology studies, which often rely on central-site air monitors?**
    - **Provide real-time exposures for public health applications that allow people to modify their behavior and reduce their exposures (i.e., exposure management)?**
- **Relevance**
  - **Supports recommendations of NRC report (Exposure Science in 21st Century) and NAS report (Using 21st Century Science to Improve Risk-Related Evaluations) to integrate models with "big data" from wearable sensors to improve exposure assessments**

Exposure Model for Individuals (EMI)
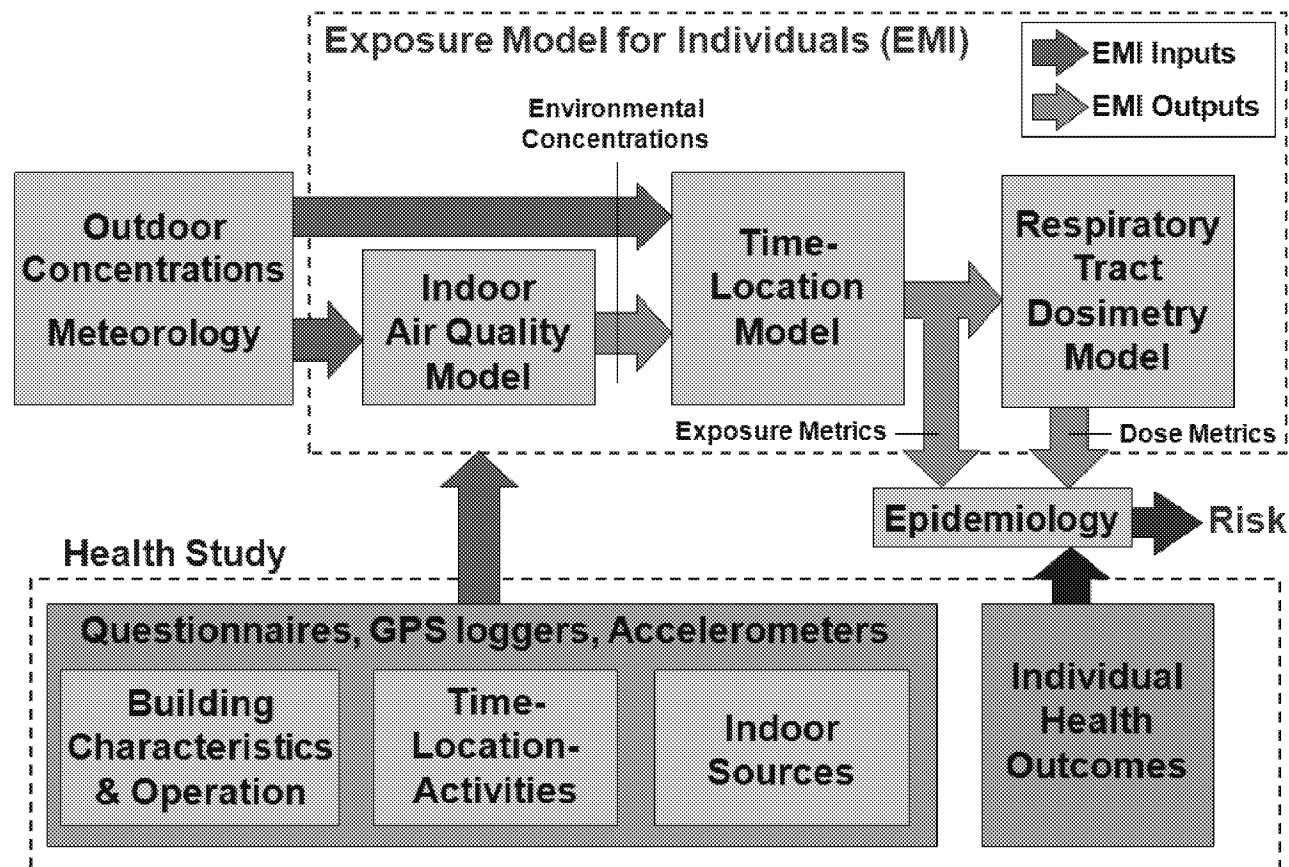
Applications of EMI for Epidemiology

- EMI accounts for (1) time- and building-specific attenuation of ambient air pollutants, (2) time spent in different microenvironments (e.g., outdoors and indoors at home, work, school; in-vehicles)

- EMI exposure predictions used for epidemiological analysis

- EMI applied for multiple air pollution epidemiology studies:
  - DEPS – Type 2 diabetes cohort in central North Carolina
  - NEXUS – Asthmatic children in Detroit, Michigan
  - CADEE – Coronary artery disease cohort in central North Carolina
  - PISCES – Protective effects of fish oil in central North Carolina
  - MESA-Air – Cardiovascular study in multiple cities across US
  - CATHGEN – Coronary artery disease cohort in 3 NC counties

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Coronary Artery Disease and Environment Exposure (CADEE)

- **Investigating health effects of ambient fine particulate matter (PM) for individuals with coronary artery disease in central North Carolina (May 2012 – April 2014)**
- **Using integrated measurement and modeling approach to predict PM exposures for 15 participants**
- **Health outcomes:**
  - **Endothelial dysfunction via ultrasound imaging of brachial artery (indicator of artheroslerosis)**
  - **Biomarkers of inflammation, coagulation via blood samples**
  - **Heart rate variability, repolarization via ECG**

Reactive Hyperemia

Resting Diameter   Avasculorization   Dilation Diameter

Diameter

Blood Velocity

Ultrasound imaging of brachial artery
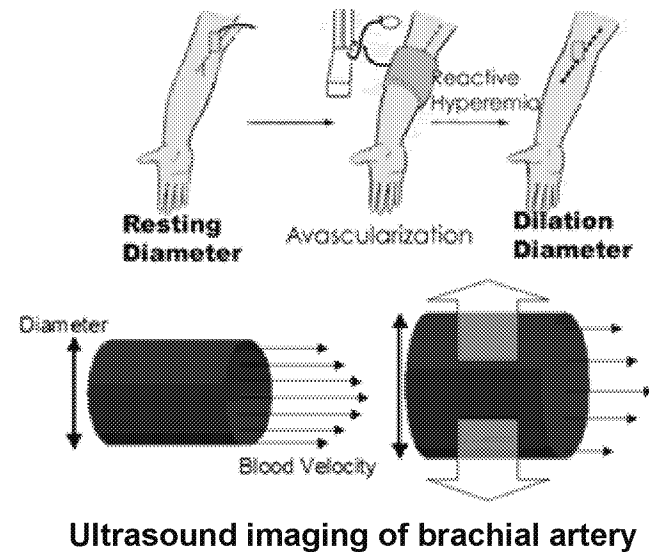
Exposure Model for Individuals (EMI)
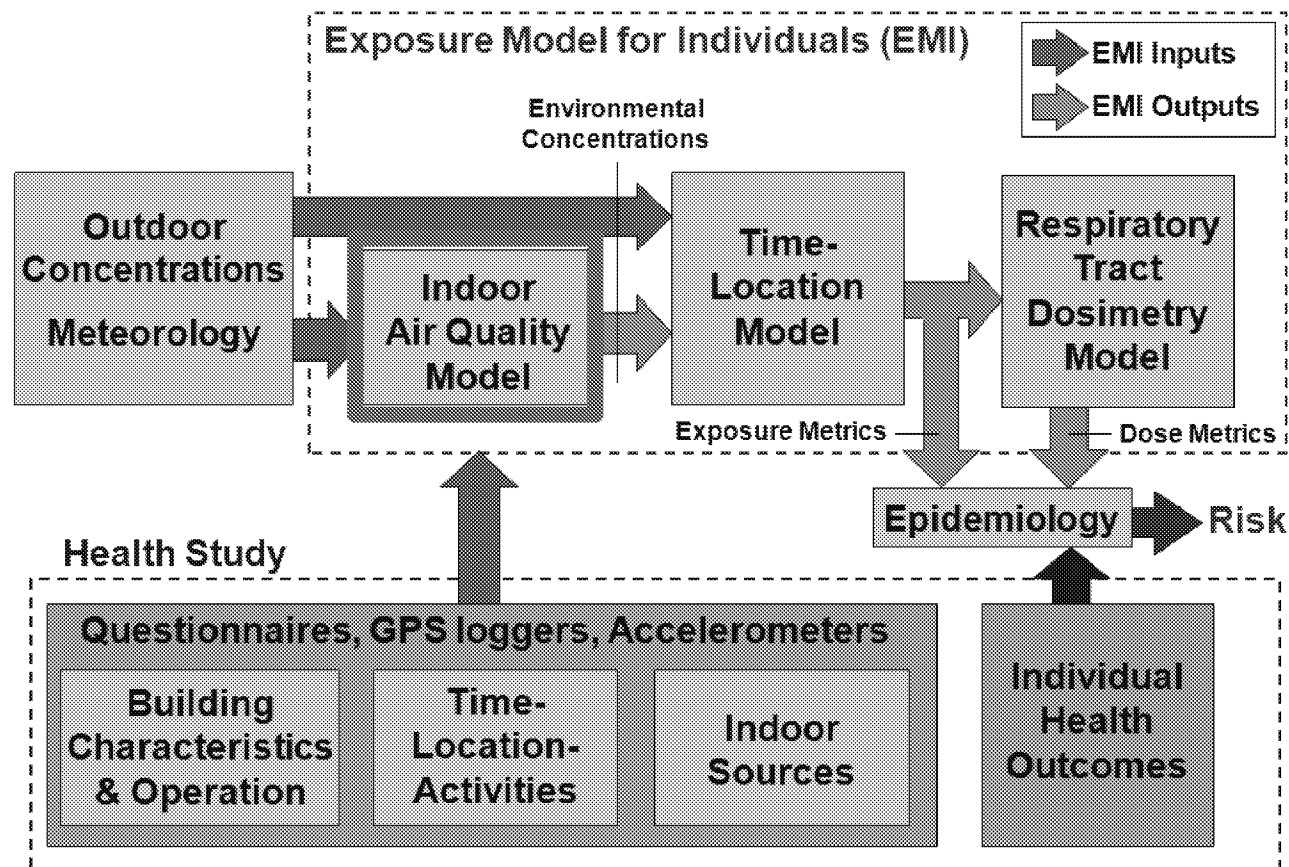
Modeled Home-Indoor Concentrations
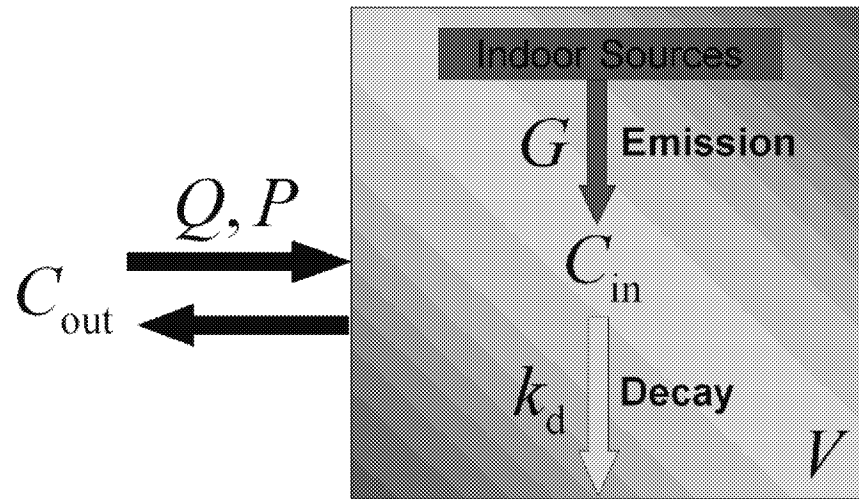
Steady-State Mass Balance Equation

$$C_{in} = \underbrace{\frac{k_a P}{k_a + k_d}}_{\text{Infiltration factor}} C_{out} + \underbrace{\frac{G}{V(k_a + k_d)}}_{\text{Indoor-generated}}$$

Infiltration factor

Outdoor-generated

Indoor-generated

Only outdoor pollutants considered in this analysis

Q, P

C_{out}

Indoor Sources

G Emission

C_{in}

k_d Decay

V

Infiltration factor accounts for indoor attenuation of outdoor conc.

Exposure Model for Individuals (EMI)
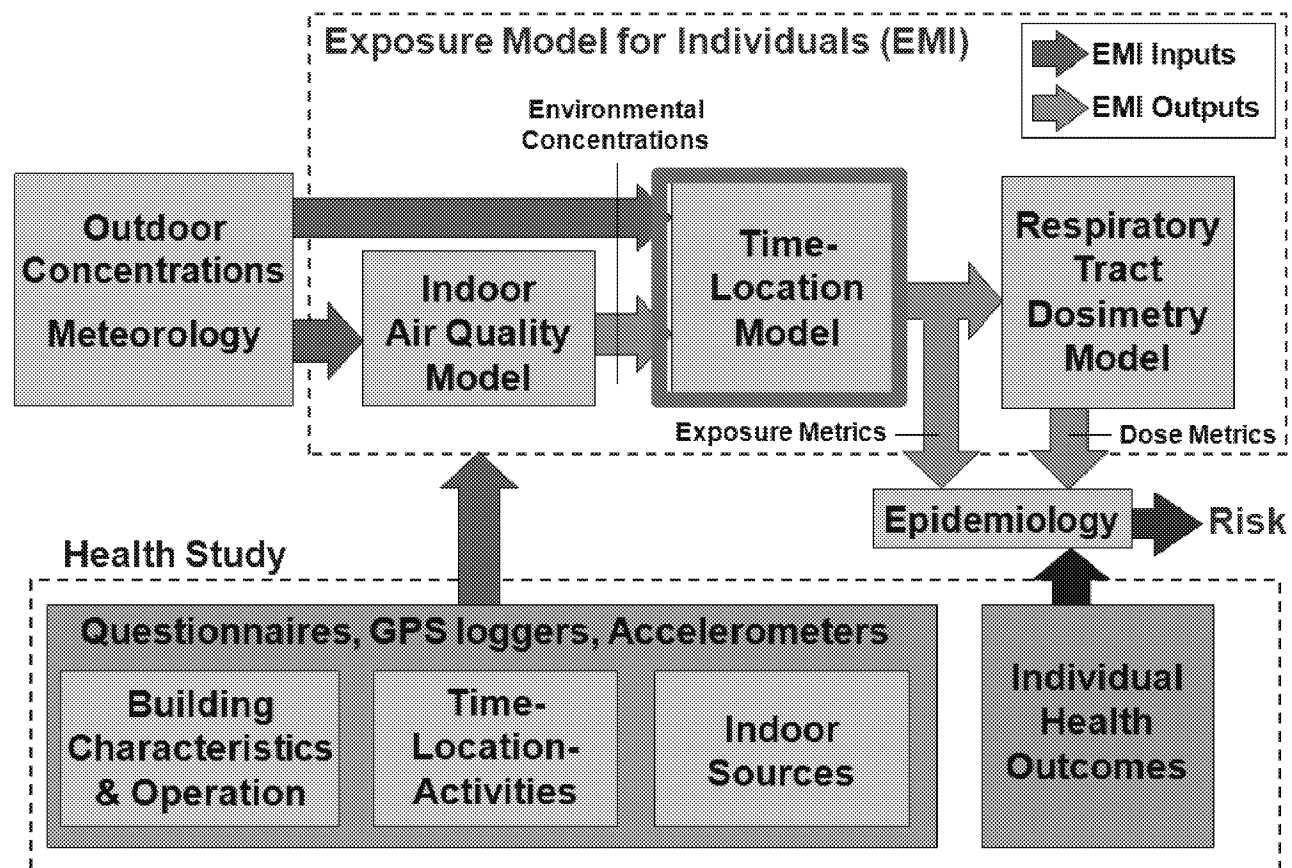
Microenvironment Tracker (MicroTrac)

Standalone GPS
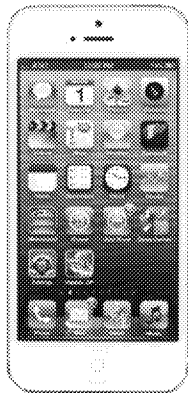
Embedded GPS in smart phones

- **Automated classification model for GPS data to estimate time spent in various microenvironments (e.g., in-vehicle, home, school, work)**
- **Addresses critical need for accurate, cost-effective, and less burdensome time-location data to improve air pollution exposure assessments**
- **Supports recommendations of NRC report (Exposure Science in 21st Century) for linking GPS data with models to:**
    - **Improve exposure assessments**
    - **Process large data from ubiquitous personal sensors**

Breen et al., J. Exp. Sci. Environ. Epidemiol. 2014

MicroTrac Design & Innovative Features

Inputs

MicroTrac

Estimated Time Spent in 8 Microenvironments

GPS Position & GPS Signal Quality

GPS Speed

Building Boundaries of Home, Work, School

Classification of GPS Samples into Microenvironments

Temporal Buffer

Temporal Filter

Spatial Buffer

Home-Indoors

Home-Outdoors

Work-Indoors

Work-Outdoors

School-Indoors

School-Outdoors

In-Vehicle

Other

Breen et al., J. Exp. Sci. Environ. Epidemiol. 2014

Fine-scale Exposure Modeling
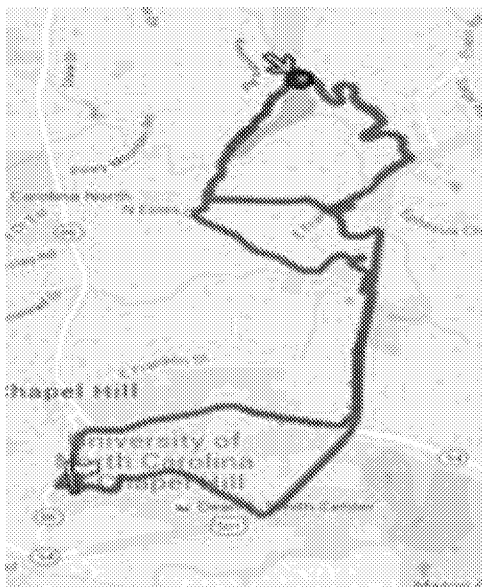
GPS Map
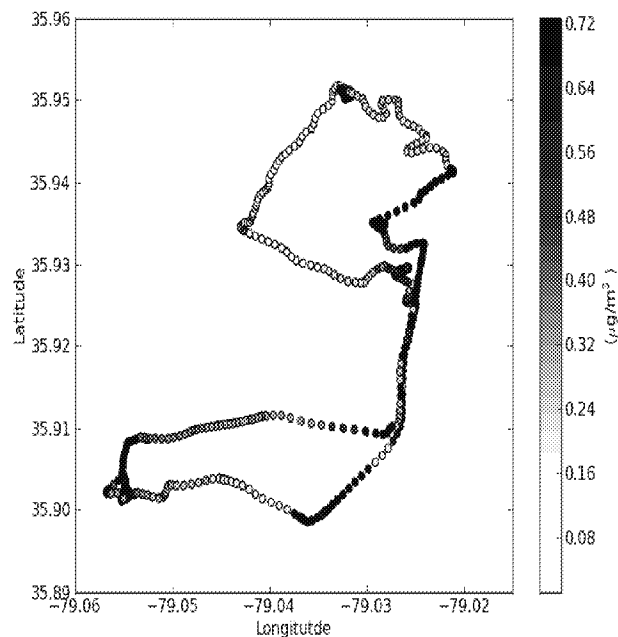
PM$_{2.5}$ Outdoors (on-road)

PM$_{2.5}$ Exposure (on-road)

ED_004465_00012138-00179
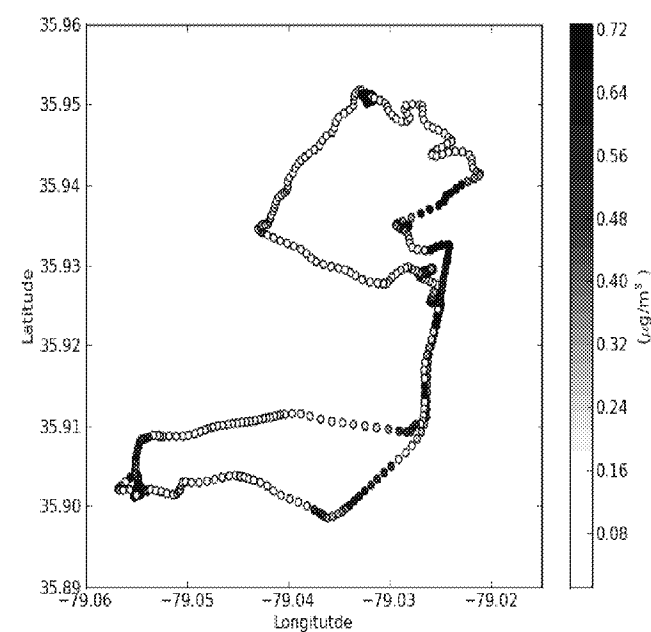
Exposure Model for Individuals (EMI)
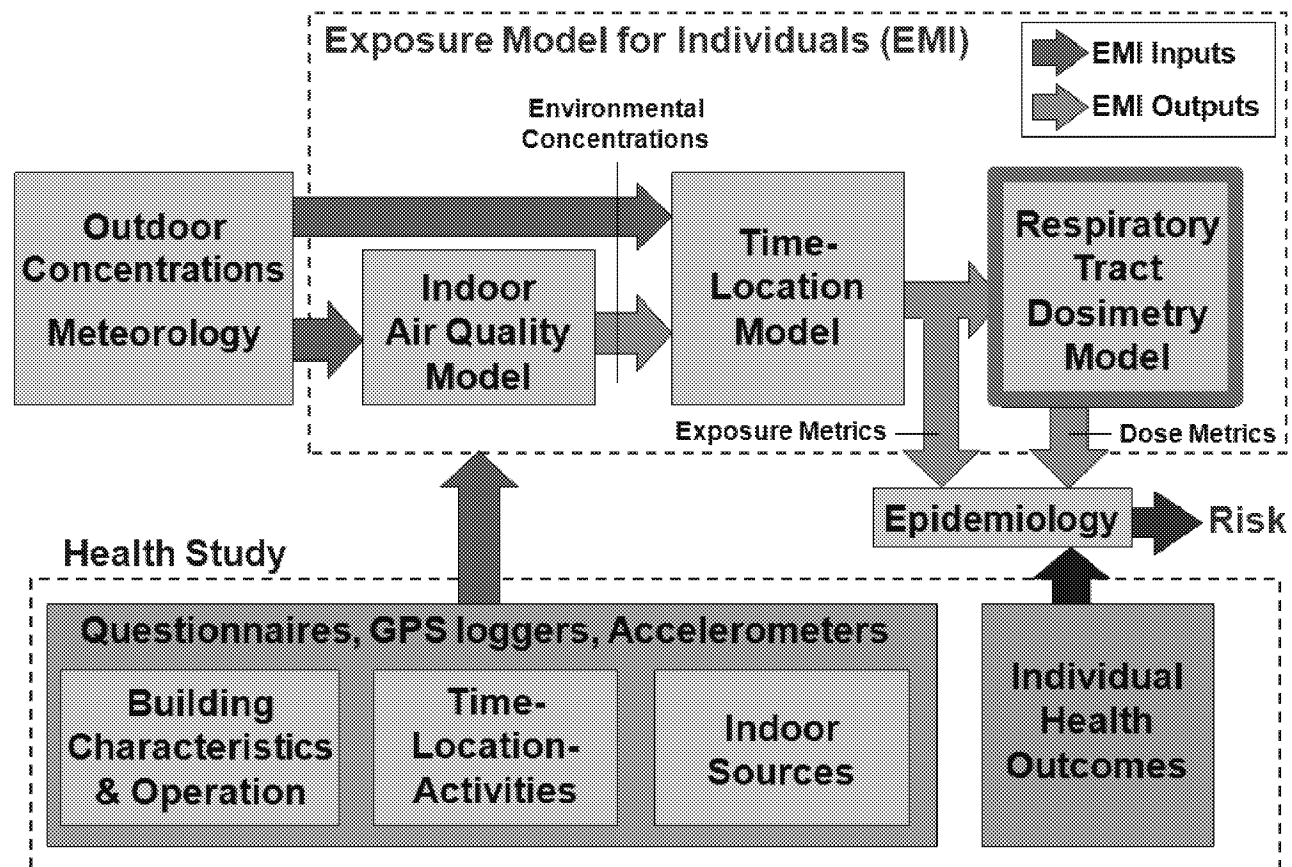
Ventilation Tracker (VTrac)

Accelerometer + GPS logger

- **Automated method to estimate minute ventilation with accelerometer data**
- **Linked with GPS-based MicroTrac allows for estimation of inhaled dose in different microenvironments**
- **Addresses critical need to account for physical activity to improve air pollution exposure assessment**

VTrac Conceptual Design

Inputs | VTrac | Estimated Physical Activity Intensities

Accelerometer Activity Counts → **Classification of Accelerometer Samples into 4 Physical Activity Intensities** → Sedentary / Light / Moderate / Vigorous

Time-matched Microenvironments from GPS-based MicroTrac →

Demographics (age, gender, weight) → **Minute Ventilation Values for each Activity Intensity** → Estimated Volume of Air Inhaled each Minute → Minute Ventilation

Dose Modeling for Each Microenvironment

- **Linked VTrac with GPS-based MicroTrac to estimate daily inhaled dose in each microenvironment**
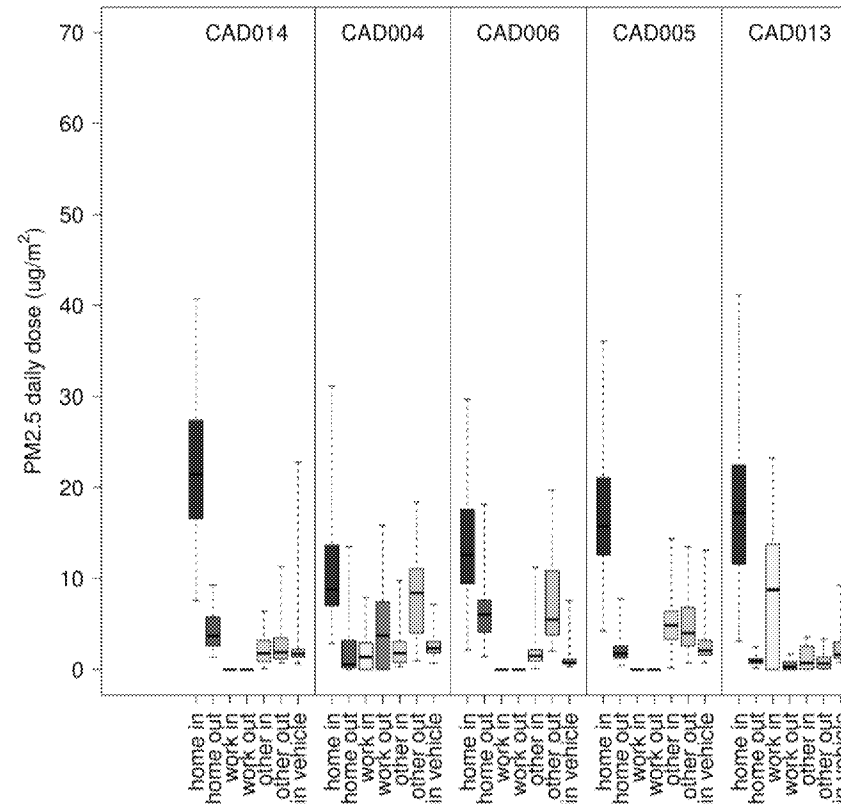
TracMyAir Mobile App
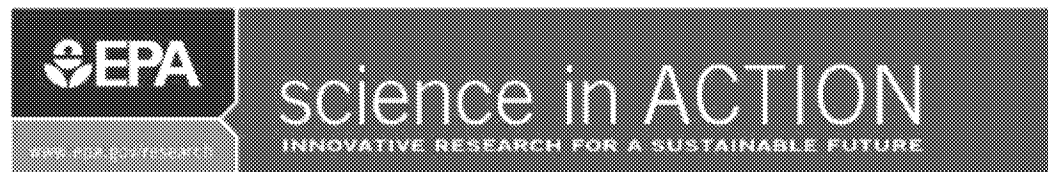
EPA's MyAir App: Using smart phones to predict near real-time air pollution exposures

Background

To better understand people's contact with air pollutants and their potential for adverse health effects, it's important to estimate how much time they spend in different locations and what the air pollutant concentrations are in those locations. Using currently available personal air monitors to collect this information has several limitations, including burden on participants, cost, and need for substantial technical expertise.

Alternatively, the currently available exposure models must be used by specially-trained researchers, and near real-time predictions are not possible since large and diverse input data (e.g., high temporally resolved air

The app uses input data available from iPhones, which includes:

* near real-time outdoor air

Microenvironment Tracker (MicroTrac), which account for time spent in different microenvironments -- such as indoors and outdoors at home,

U.S. Patent submitted

TracMyAir Mobile App

- **Use smartphone to predict near real-time air pollution exposures**

  - **Automated collection and processing of large, multidimensional model input data from smartphones (e.g., nearest air monitor, outdoor temperature and wind speed, user's location)**

  - **Home infiltration model accounts for window opening status, air cleaner usage**

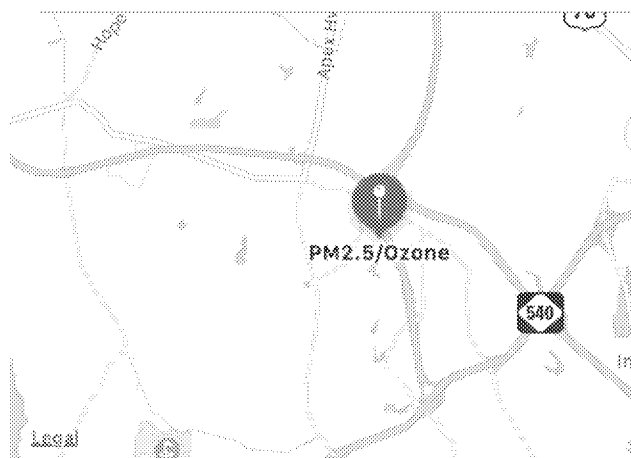 - **Accounts for attenuation of outdoor air pollution when indoors, and time spent in different microenvironments**

TracMyAir: Automated Real-time Input Data
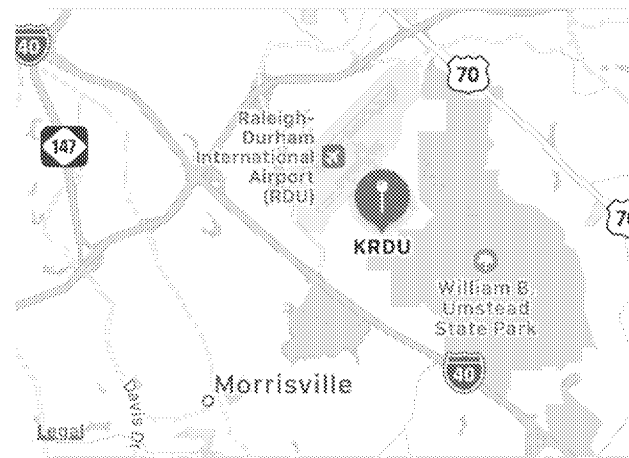
TracMyAir: Exposures (24 h avg)

Main App Screen

Exposures

App execution time: 5-10 s

TracMyAir: Exposure/Dose for Each Microenvironment

Indoors at home
▪▪ Verizon 📶   2:12 PM   ◹ 50% 🔋

< Back   **Indoors at home**

Time spent indoors at home	13:15 / 55.21%
PM2.5 exposure	3.2 µg/m³ / 48.01%
PM2.5 dose	19.7 µg/m² / 33.55%
Ozone exposure	1.32 ppb / 27.94%
Ozone dose	16.2 µg/m² / 11.62%

Indoors at school
▪▪ Verizon 📶   2:28 PM   ◹ 49% 🔋

< Back   **Indoors at school**

Time spent indoors at school	0:00 / 0.00%
PM2.5 exposure	0.0 µg/m³ / 0.00%
PM2.5 dose	0.0 µg/m² / 0.00%
Ozone exposure	0.00 ppb / 0.00%
Ozone dose	0.0 µg/m² / 0.00%

Inside vehicles
▪▪ Verizon 📶   2:12 PM   ◹ 50% 🔋

< Back   **Inside vehicles**

Time spent inside vehicles	1:00 / 4.17%
PM2.5 exposure	0.2 µg/m³ / 3.17%
PM2.5 dose	1.1 µg/m² / 1.83%
Ozone exposure	0.29 ppb / 6.09%
Ozone dose	2.9 µg/m² / 2.10%

Indoors at work
▪▪ Verizon 📶   2:13 PM   ◹ 50% 🔋

< Back   **Indoors at work**

Time spent indoors at work	7:45 / 32.29%
PM2.5 exposure	2.3 µg/m³ / 35.72%
PM2.5 dose	14.9 µg/m² / 25.34%
Ozone exposure	1.16 ppb / 24.64%
Ozone dose	14.5 µg/m² / 10.40%

Indoors at other
▪▪ Verizon 📶   2:28 PM   ◹ 49% 🔋

< Back   **Indoors at other**

Time spent indoors at other	0:30 / 2.08%
PM2.5 exposure	0.2 µg/m³ / 2.30%
PM2.5 dose	3.3 µg/m² / 5.67%
Ozone exposure	0.07 ppb / 1.59%
Ozone dose	3.2 µg/m² / 2.33%

Outdoors
▪▪ Verizon 📶   2:12 PM   ◹ 51% 🔋

< Back   **Outdoors**

Time spent outdoors	1:30 / 6.25%
PM2.5 exposure	0.7 µg/m³ / 10.80%
PM2.5 dose	19.7 µg/m² / 33.60%
Ozone exposure	1.88 ppb / 39.74%
Ozone dose	102.6 µg/m² / 73.56%

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TracMyAir: Dose for Each Physical Activity Intensity

Sedentary Intensity (2:59 PM)

Sedentary intensity time	17:30 / 72.92%
Activity time outdoors	0:00
Activity time inside vehicles	1:00
Activity time indoors at work	6:00
Activity time indoors at school	0:00
Activity time indoors at other	0:00
Activity time indoors at home	10:30
PM2.5 dose	22.6 µg/m² / 39.86%
Ozone dose	22.9 µg/m² / 16.29%
Minute ventilation	3.59 L/min/m²

Light Intensity (2:59 PM)

Light intensity time	4:30 / 18.75%
Activity time outdoors	0:00
Activity time inside vehicles	0:00
Activity time indoors at work	1:45
Activity time indoors at school	0:00
Activity time indoors at other	0:00
Activity time indoors at home	2:45
PM2.5 dose	11.9 µg/m² / 20.87%
Ozone dose	11.0 µg/m² / 7.82%
Minute ventilation	7.18 L/min/m²

Moderate Intensity (2:58 PM)

Moderate intensity time	1:30 / 6.25%
Activity time outdoors	1:00
Activity time inside vehicles	0:00
Activity time indoors at work	0:00
Activity time indoors at school	0:00
Activity time indoors at other	0:30
Activity time indoors at home	0:00
PM2.5 dose	13.3 µg/m² / 23.38%
Ozone dose	57.8 µg/m² / 41.10%
Minute ventilation	15.26 L/min/m²

Vigorous Intensity (2:58 PM)

Vigorous intensity time	0:30 / 2.08%
Activity time outdoors	0:30
Activity time inside vehicles	0:00
Activity time indoors at work	0:00
Activity time indoors at school	0:00
Activity time indoors at other	0:00
Activity time indoors at home	0:00
PM2.5 dose	9.0 µg/m² / 15.89%
Ozone dose	48.9 µg/m² / 34.79%
Minute ventilation	27.37 L/min/m²

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Applications of TracMyAir

- **Current application: Two epidemiological studies in central North Carolina (PISCES)**

  - **Automated, real-time predictions of individual exposures**

  - **Facilitate and expand use of modeled exposure metrics for epidemiology studies**

- **Potential future application: Public health**

  - **Provides timely personalized notifications of exposure for susceptible individuals**

  - **Allows people to modify their behavior (e.g., go indoors, close windows, reduce activity level, operate home air cleaner)**
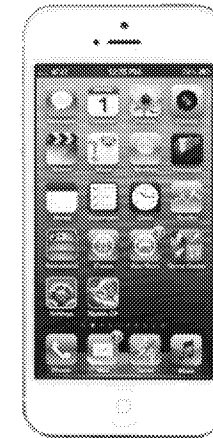
Acknowledgments

Model Design & Evaluation Teams

EMI – Exposure Model for Individuals
AER – Residential air exchange rate
MicroTrac – Microenvironment Tracker
VTrac – Ventilation Tracker
TracMyAir – Mobile App

Epidemiology & Field Study Teams

RTP PM Panel Study
NEXUS – asthma cohort
DEPS – diabetes cohort
CADEE – cardiovascular disease cohort
MESA Air – arteriosclerosis cohort
PISCES – fish oil cohort
CATHGEN – coronary catheterization cohort
OMEGOZ – fish consumption study

EPA Collaborators

ORD: NERL, NHEERL, NCEA, NCER
Program Offices: OAR: OAQPS, ORIA

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Helmholtz Zentrum Munchen, Germany
Alexandra Schneider

Emory University
Jeremy Sarnat

Harvard University
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North Carolina State University
H. Christopher Frey

University of Washington
Joel Kaufman

Duke University
CATHGEN Study Team

University of North Carolina
Sarav Arunachalam

Boston University
Jonathan Levy

University of Michigan
Stuart Batterman

Illinois Institute of Technology
Brent Stephens

Systematic review of nutrient stressor-response relationships in running waters

Micah Bennett, Sylvia Lee, Kate Schofield, Caroline Ridley, and Sue Norton

1. *What are the responses of* **chlorophyll-a**, **diatoms**, *and* **macroinvertebrates** *to* **TN** *and* **TP** *concentrations in lotic ecosystems?*

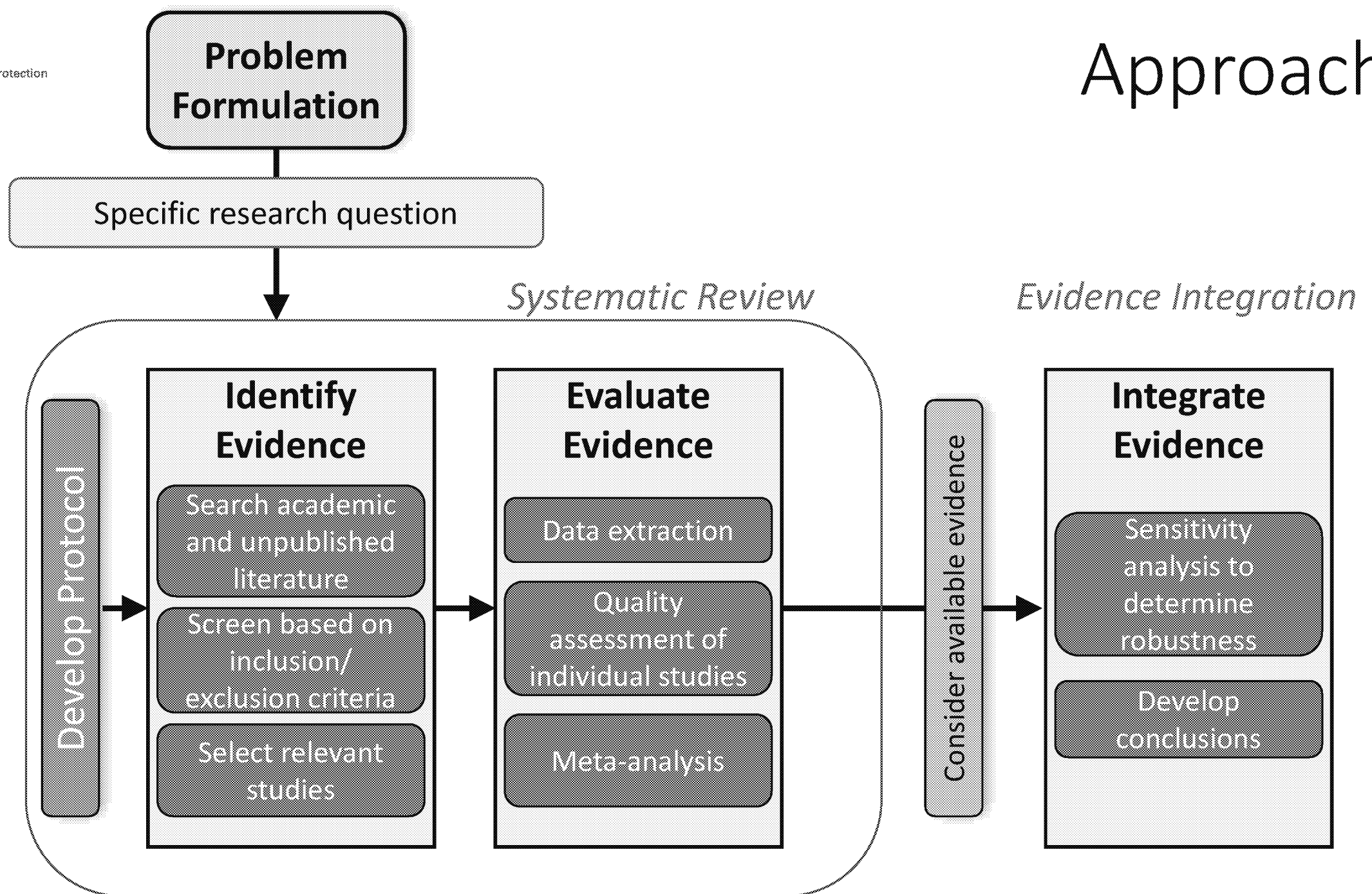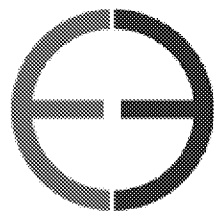2. *How are these relationships affected by other factors?*
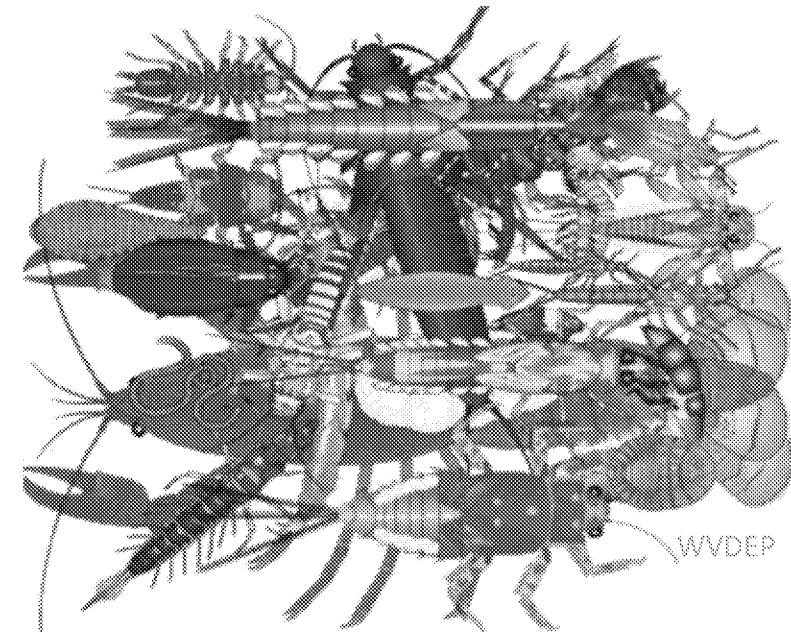
- Project overview

- Approach

- Implications of study design

- Types of questions addressed

S. Lee

M. Bennett

Approach

Adapted from Boyles et al. 2016, OHAT/NTP/NIEHS

Collaboration for Environmental Evidence
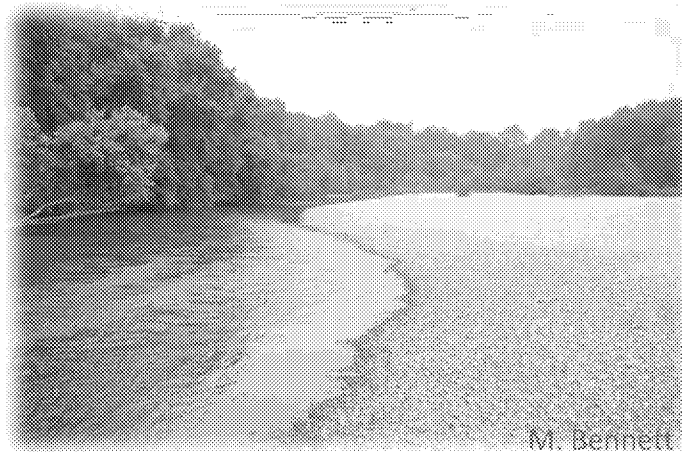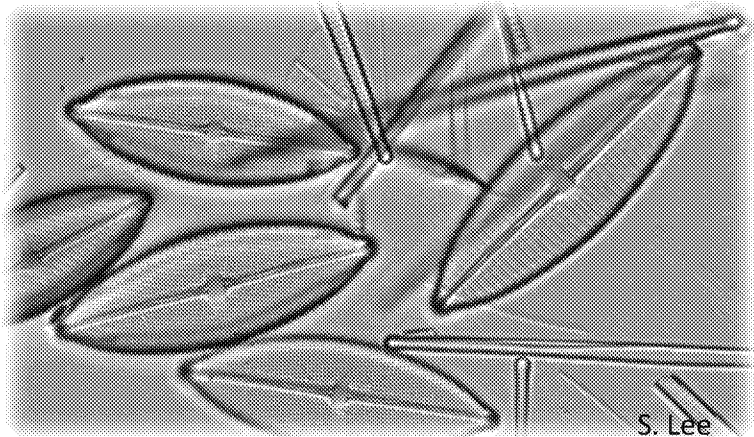
An open community of stakeholders working towards a sustainable global environment and the conservation of biodiversity. CEE seeks to promote and deliver evidence syntheses on issues of greatest concern to environmental policy and practice as a public service.

Environmental Evidence
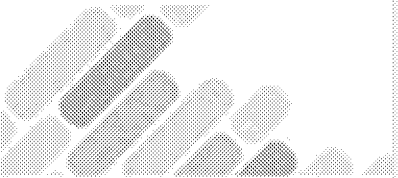
Bennett et al. Environ Evid (2017) 6:18
DOI 10.1186/s13750-017-0097-8

Environmental Evidence

SYSTEMATIC REVIEW PROTOCOL — Open Access

CrossMark

Response of chlorophyll *a* to total nitrogen and total phosphorus concentrations in lotic ecosystems: a systematic review protocol

Micah G. Bennett, Kate A. Schofield, Sylvia S. Lee and Susan B. Norton

GUIDELINES for SYSTEMATIC REVIEWS in ENVIRONMENTAL MANAGEMENT

New version 5.0 published 2018

Search

ProQuest ES   Scopus   JSTOR   CAB   Wiley   BioOne   State/fed/int'l env agencies   Google   ResearchGate   Twitter   ECOLOG-L

Ingenta
ScienceDirect
Greenfile

22,488
from academic databases

3,398
from 'snowball' searches

691
from website searches

83
from expert requests

AGRICOLA   Web of Science   ProQuest D&T AGRIS   NGOs OpenGrey   NTRL DART

TOTAL INPUT = 26,660 citations

Screen

>25,000
excluded

~1000
w/ no clear
effect size

Data extraction
Quality evaluation

Extract &
Synthesize

306
Full-text articles w/ effect
sizes for data extraction &
quality evaluation

TN   chl-a
TP   diatoms
          bugs
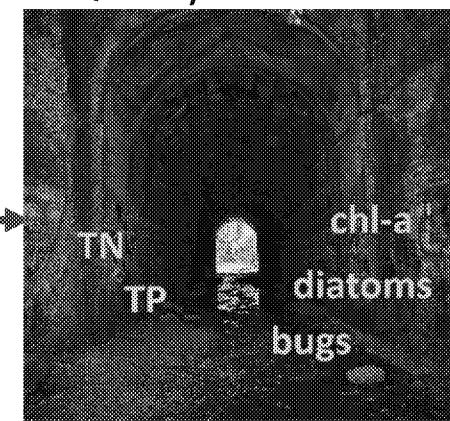
Meta-analysis
Synthesis

DRAFT

Cause
(TN, TP)

Effect
(chl, diatoms, macros)

DRAFT

Cause
(TN, TP)

Effect
(chl, diatoms, macros)

term
measure
trajectory
units
range
mean/median
standard deviation
transformations

response measure value
response measure type
documentation
response equation
response form

term
measure
measure detail
trajectory
units
range
chl extraction & meas.
mean/median
standard deviation
transformations

Data Extraction

EPA
United States
Environmental Protection
Agency

Study Design

term
measure
trajectory
units
range
mean/median
standard deviation
transformations

response measure value
response measure type

Cause
(TN, TP)

documentation
response form

response equation

Effect
(chl, diatoms, macros)

term
measure
measure detail
trajectory
units
range
chl extraction & meas.
mean/median
standard deviation
transformations

CITATION ID
AUTHOR(S)
YEAR
DATASET ID
SOURCE DATA
STUDY TYPE
STUDY DESIGN
SAMPLE SELECTION
CONTROL SAMPLES
CONTROL REPLICATES
IMPACT SAMPLES
IMPACT REPLICATES

In-stream factors

pH
sediment load
suspended sediment
temperature
alkalinity
discharge
flow permanence
velocity
dissolved oxygen
turbidity

light
canopy cover
conductivity
elevation
habitat
dominant substrata
channel width
dissolved organic C
water depth
dissolved nutrient conc.

Regional/landscape factors

climate
dominant land use
latitude/longitude
stream order
watershed area
ecoregion
precipitation
elevation
slope/gradient

Other context

state/province
country
sample year
sample month
temporal extent
spatial extent

Modifying/confounding factors

DRAFT

ED_004465_00012138-00201

Field observational
- Study design & sampling
- Data analysis & results
- Other biases

Mesocosm experiment
- Study design & sampling
- Data analysis & results
- Other biases

Field experiment
- Study design & sampling
- Data analysis & results
- Other biases
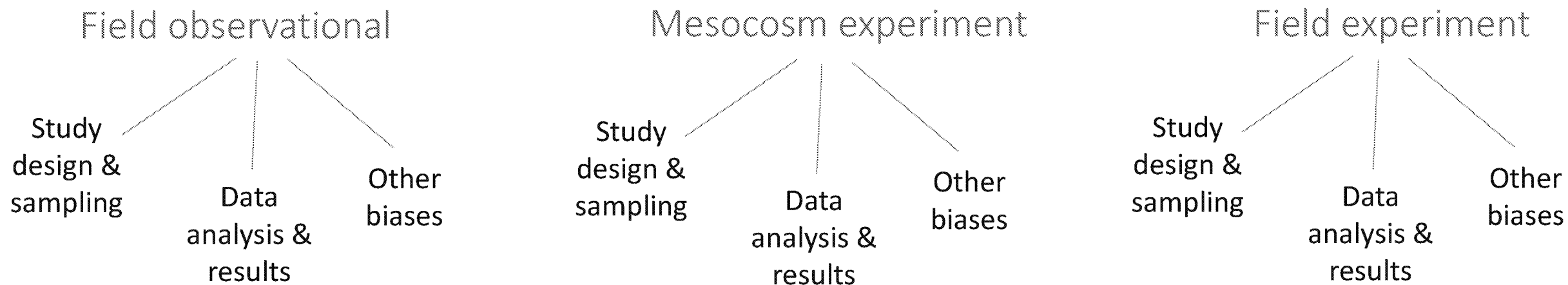
Elements compiled from:

Mupepele A-C, Walsh JC, Sutherland WJ, Dormann CF. An evidence assessment tool for ecosystem services and conservation studies. Ecological Applications 26:1295–1301.

Bilotta GS, Milner AM, Boyd IL. Quality assessment tools for evidence from environmental science. Environmental Evidence 2014;3:14. (adaptation of GRADE)

Higgins J, Green S, editors. Cochrane handbook for systematic reviews of interventions. Version 5. The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org.

Selection bias
Performance bias
Attrition bias
Detection bias
Reporting bias

Statistical validity
Clarity

DRAFT

Evidence base includes few experimental ('high quality') studies – true of many ecological questions
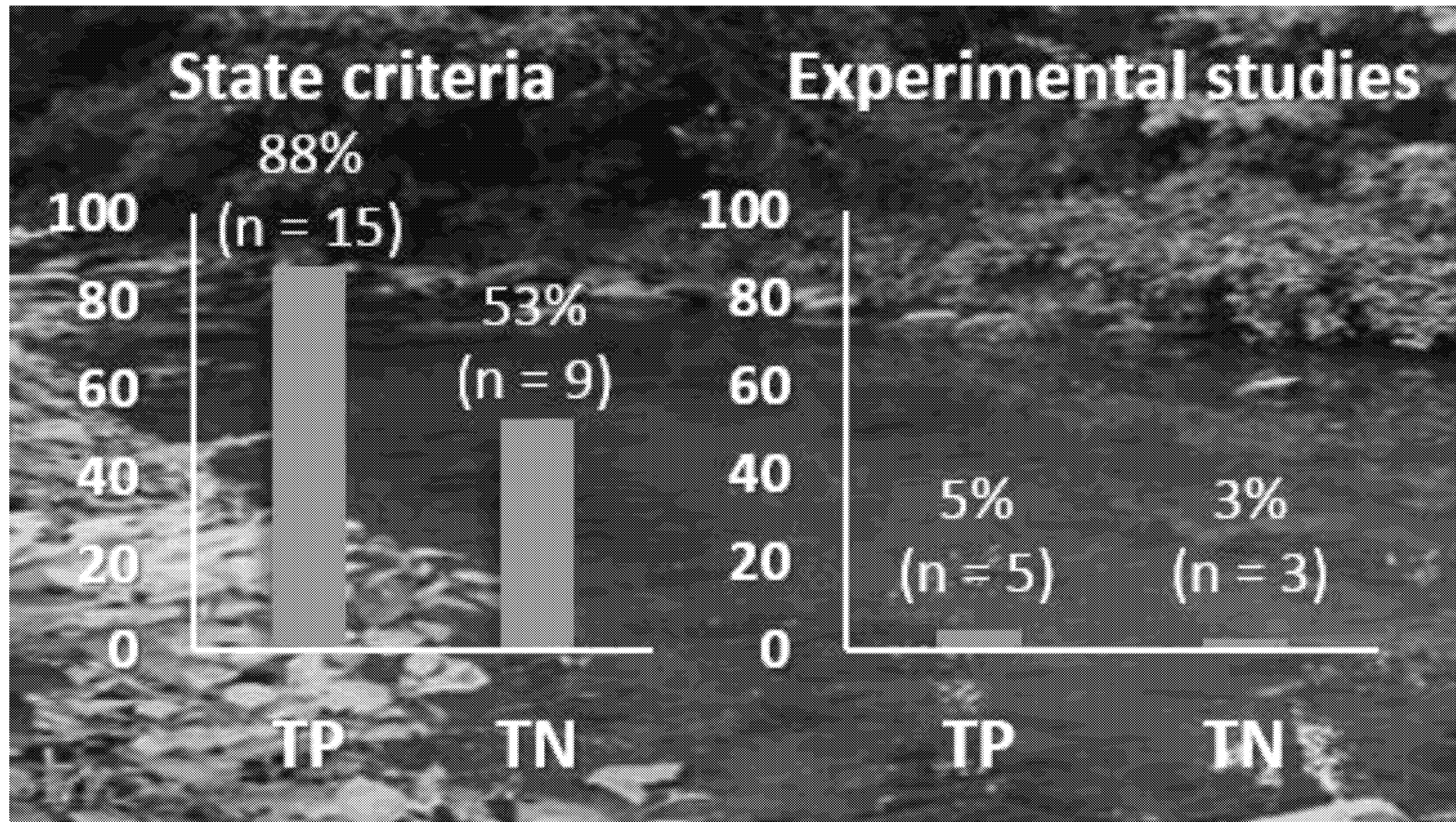
min TP
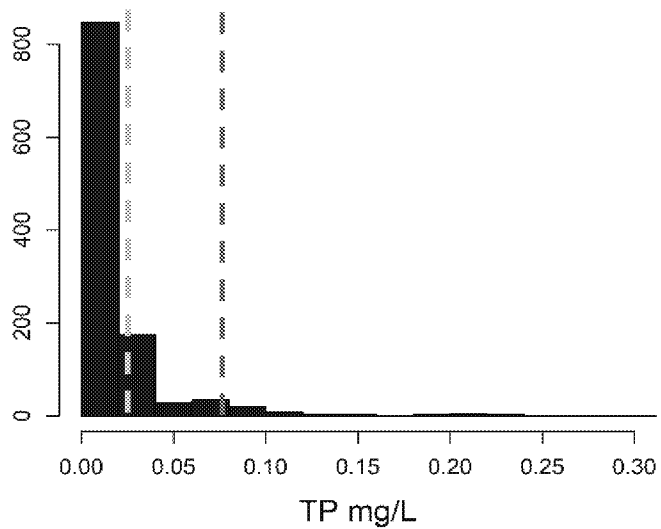
mean TP
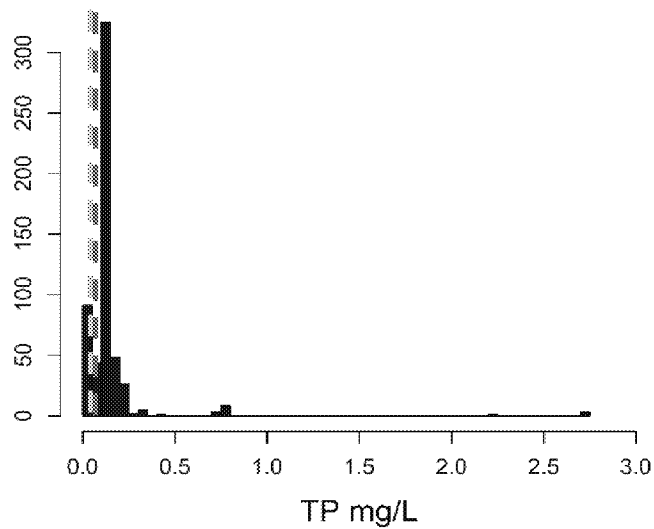
median TP

max TP

Stream Trophic Classification - Dodds et al. 1998

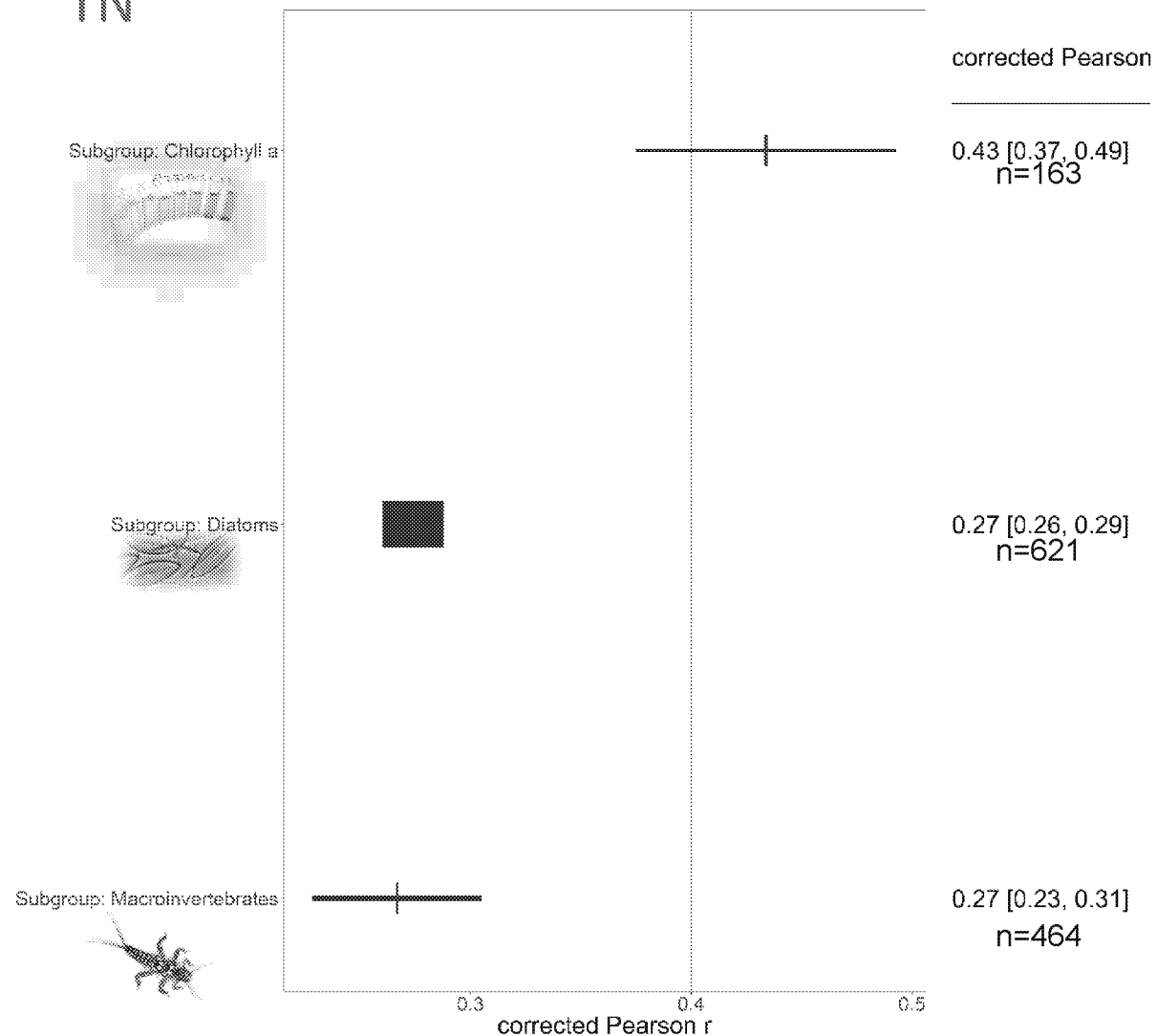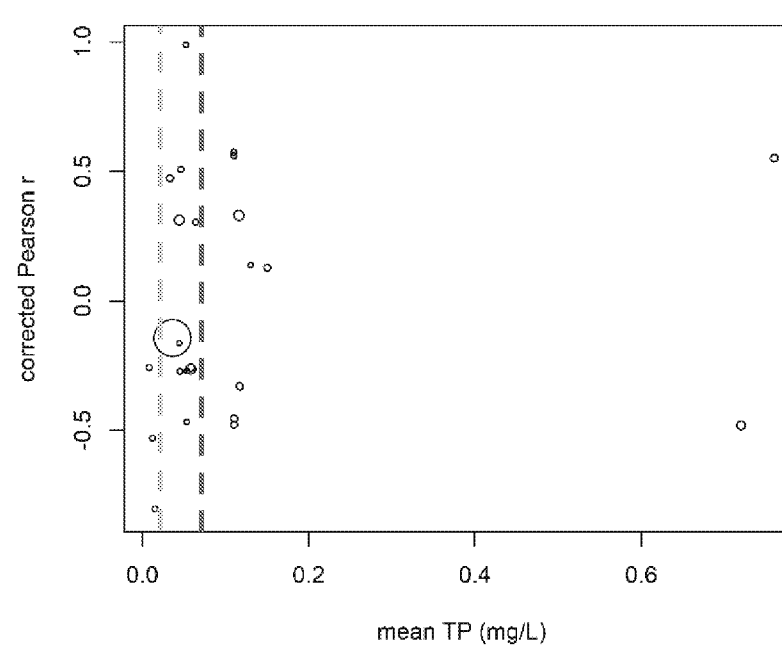| TP 0.025 mg/L	TP 0.075 mg/L
TN 0.7 mg/L	TN 1.5 mg/L

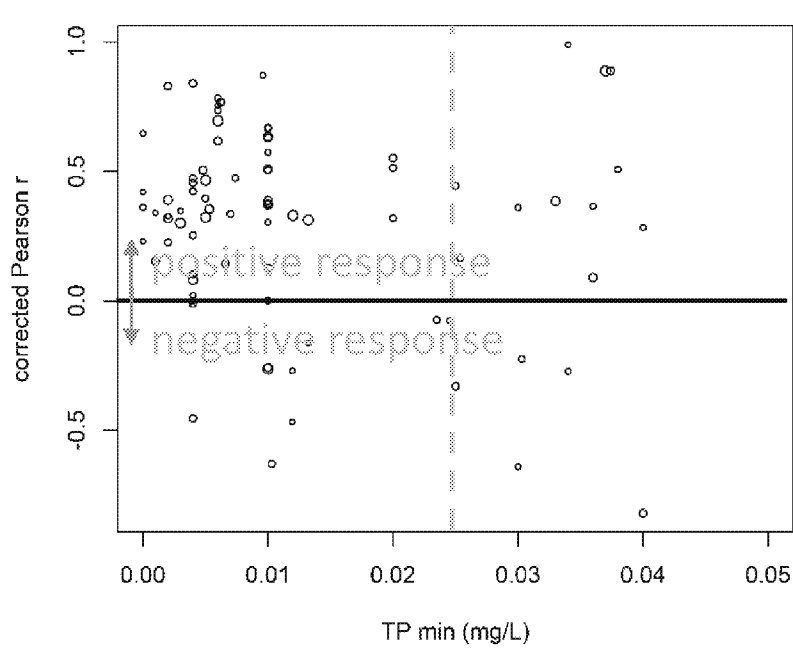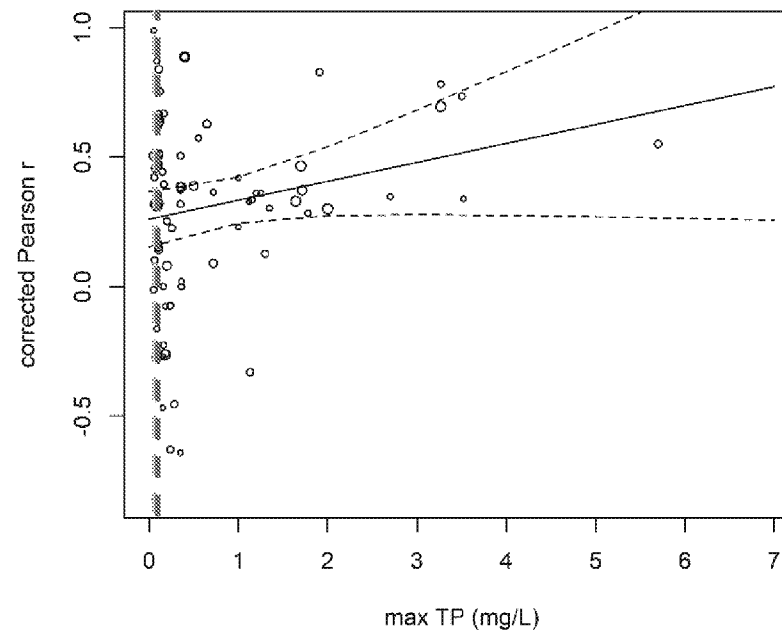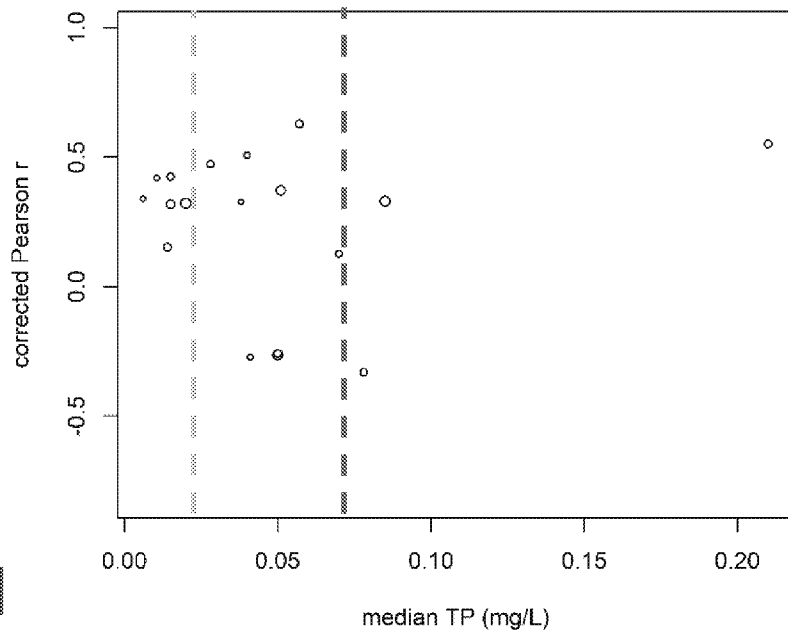oligotrophic   mesotrophic   eutrophic
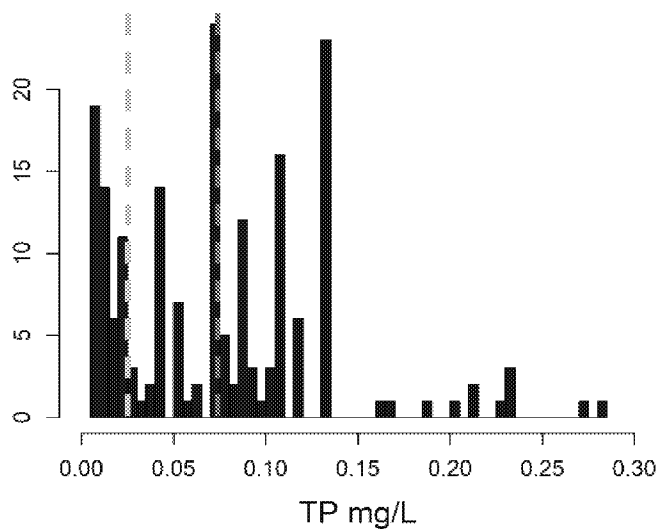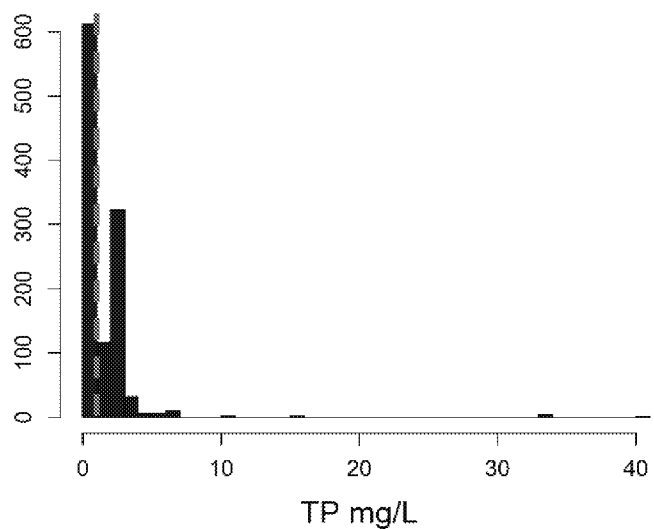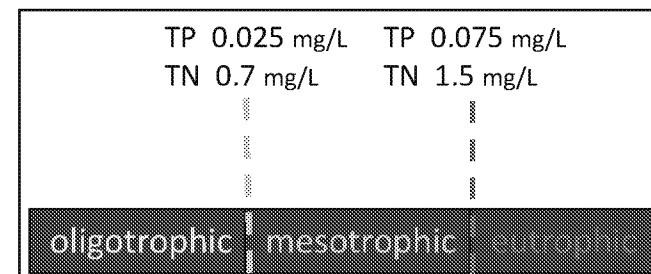
How do biota respond to stressors?
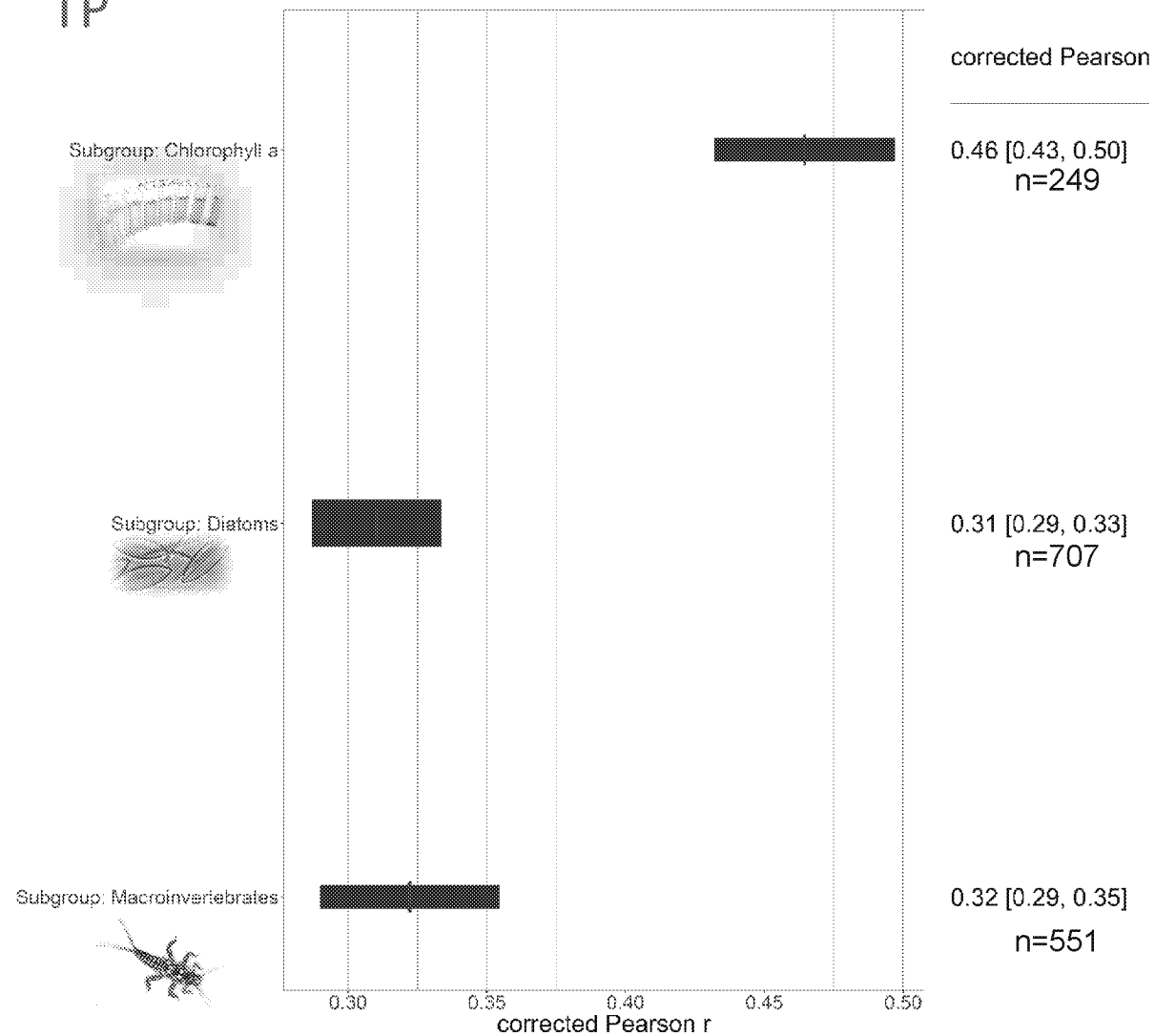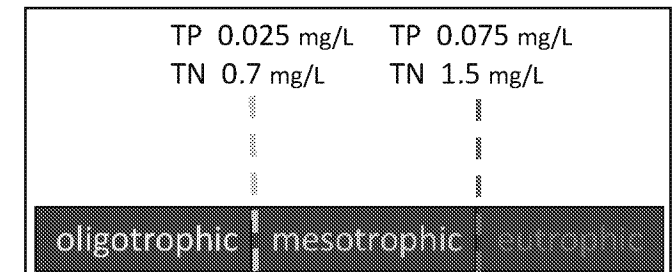
(absolute value of Pearson r)

How does the strength of response change across an exposure gradient?

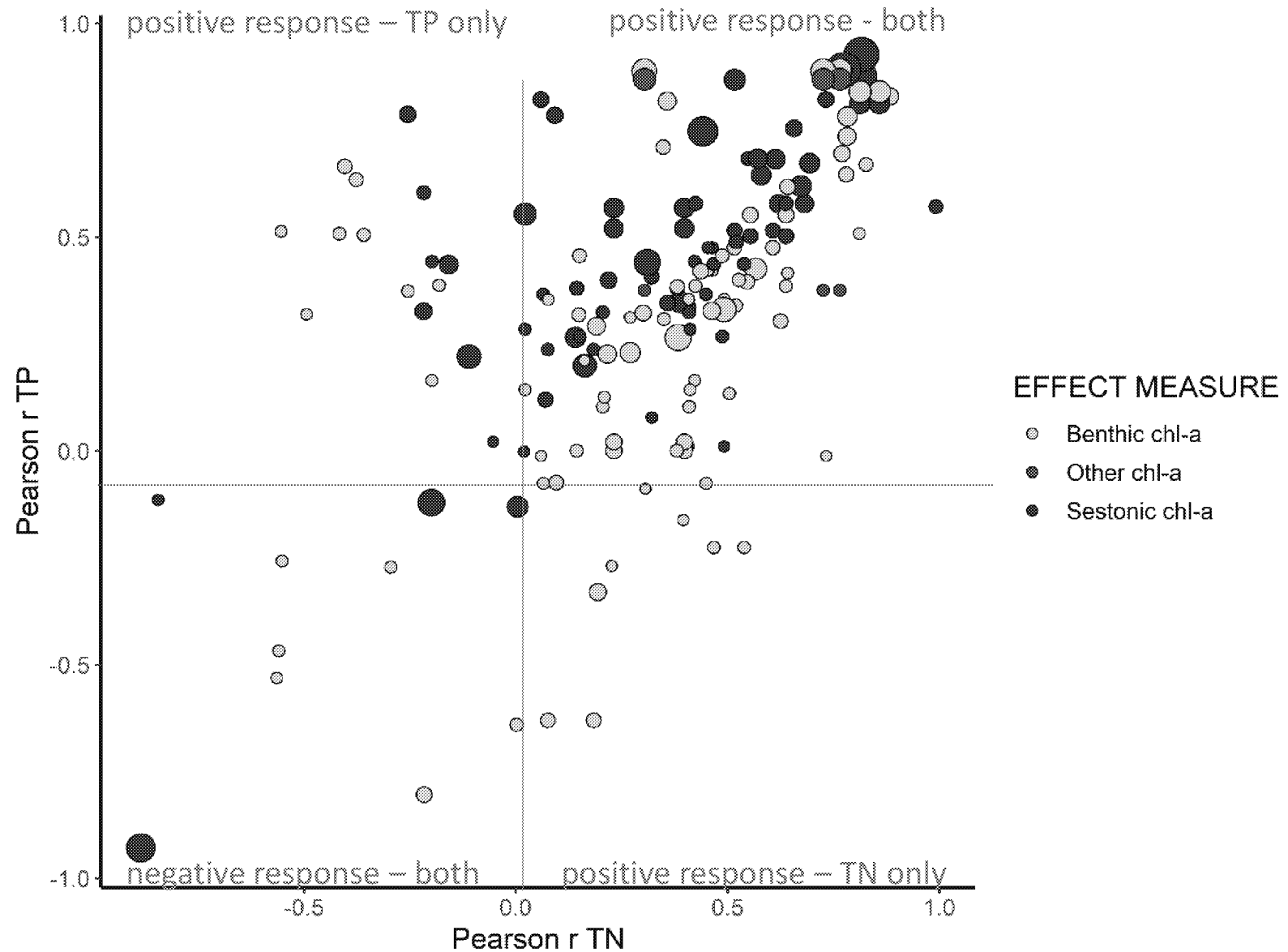Benthic chl & TP

Stream Trophic Classification - Dodds et al. 1998
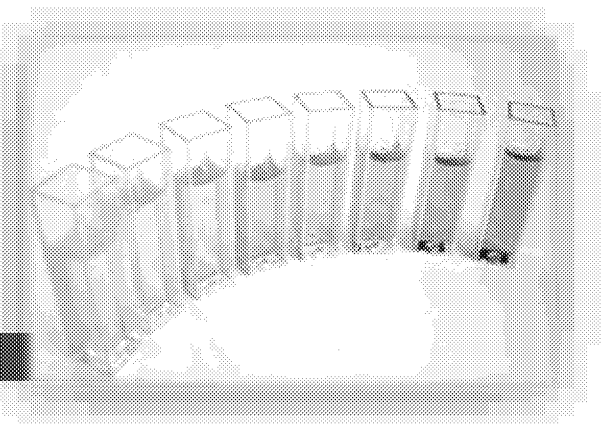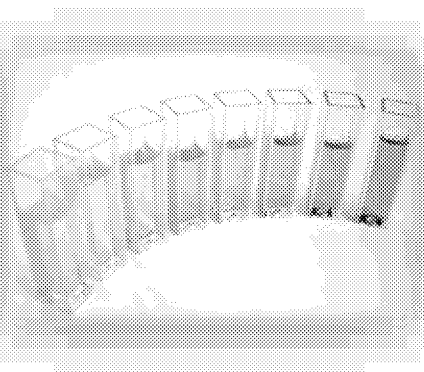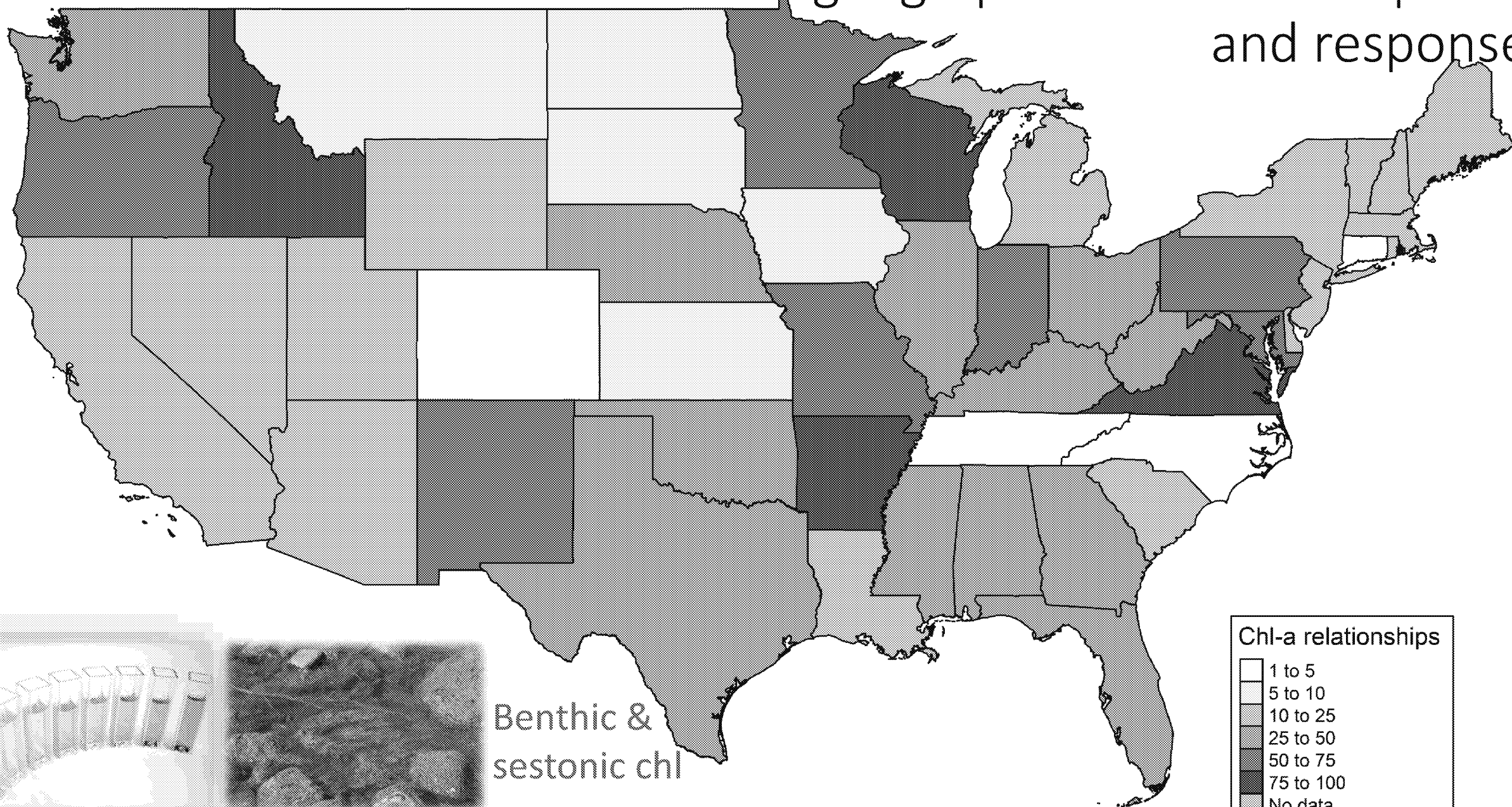
	TP 0.025 mg/L	TP 0.075 mg/L
	TN 0.7 mg/L	TN 1.5 mg/L

oligotrophic mesotrophic eutrophic

What is the geographic context of exposure and response?

Benthic & sestonic chl

Chl-a relationships
- 1 to 5
- 5 to 10
- 10 to 25
- 25 to 50
- 50 to 75
- 75 to 100
- No data

Benthic chl & TP

EPA
United States
Environmental Protection
Agency
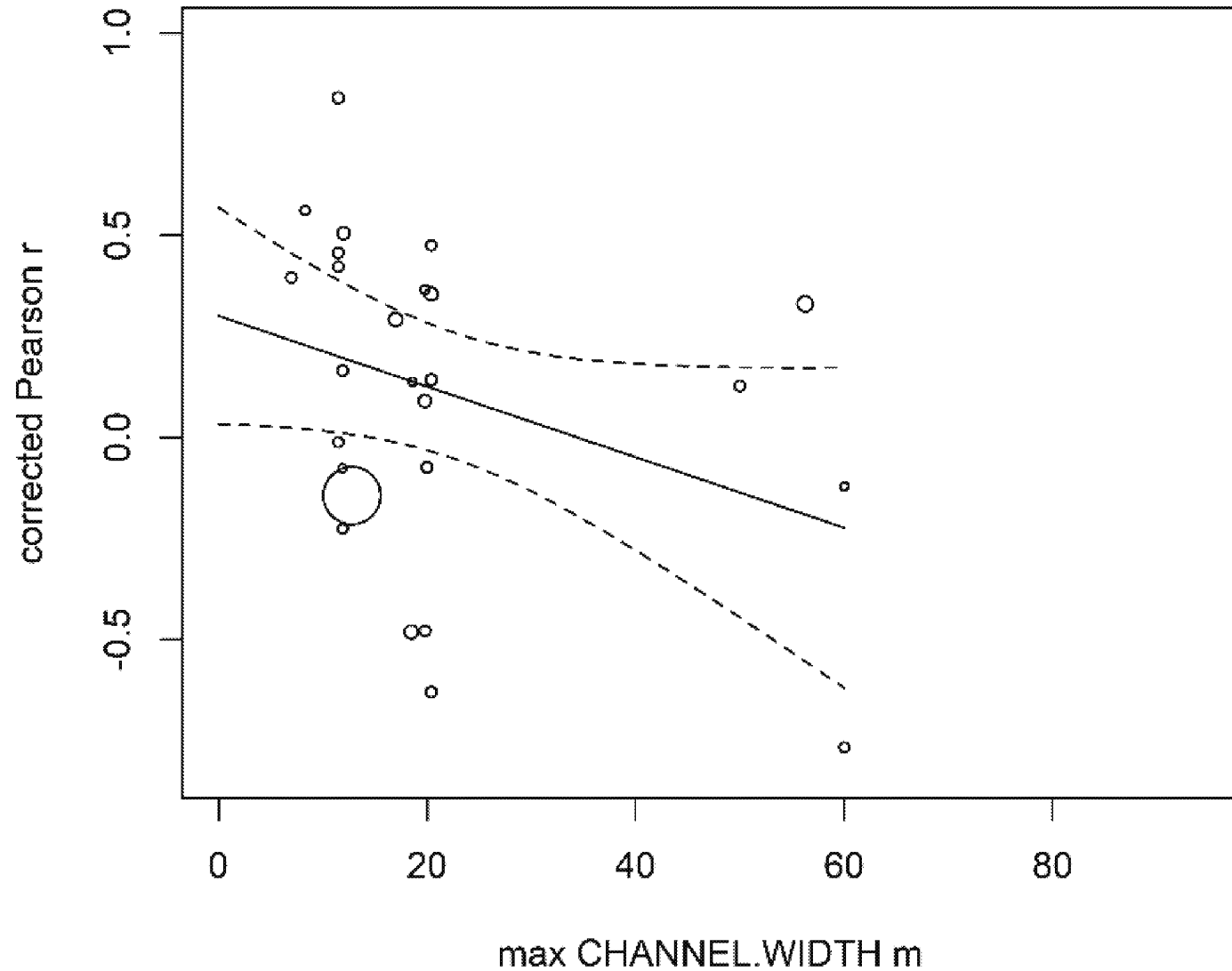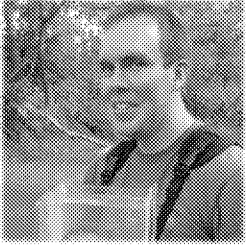
Micah Bennett
bennett.micah@epa.gov

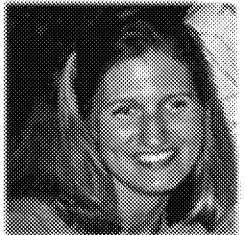
Caroline Ridley
ridley.caroline@epa.gov
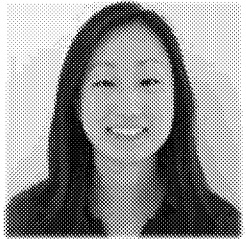
Sylvia Lee
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Kate Schofield
schofield.kate@epa.gov

DRAF

Using the OHAT Approach to Reach Conclusions Across Multiple Exposures

Brandy Beverly, PhD
National Toxicology Program
US National Institute of environmental Health Sciences

April 25, 2019

Systematic Review In Exposure Science Summit

NTP Office of Health Assessment and Translation

- OHAT serves as an environmental health resource for public and regulatory agencies

- Conduct literature-based evaluations to assess the evidence that environmental substances cause adverse health effects
  - Systematic review (SR)
  - Evidence mapping

- Promote SR methods development and uptake in environmental health
  - Encourage harmonization
  - Engage collaboration for ongoing challenges

…challenges like exposure

NTP Monographs
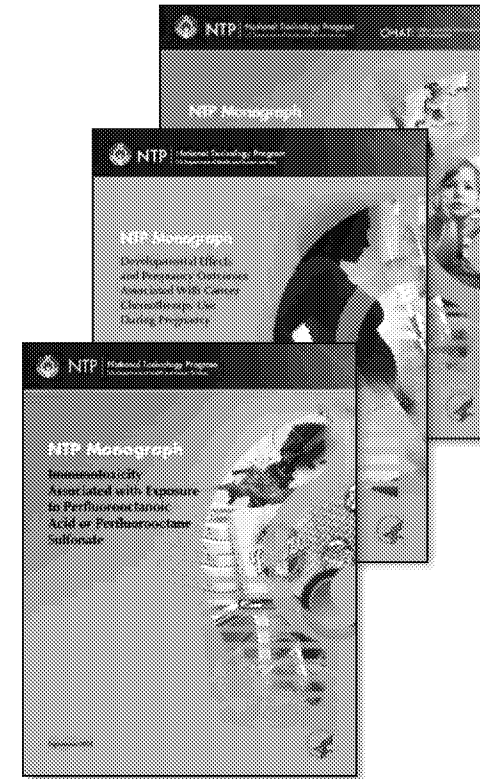
NTP Reports

Workshops
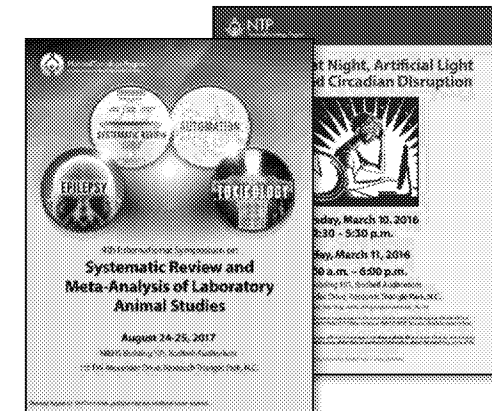
- Systematic review approaches are highly effective at transparently evaluating evidence on groups of studies addressing the same or similar endpoints

- Broad topics like "**Is PM$_{2.5}$ associated with cardiovascular toxicity?**" can be addressed with series of specific questions

  - All cardiovascular endpoints ➡ Hypertension ➡ Blood Pressure
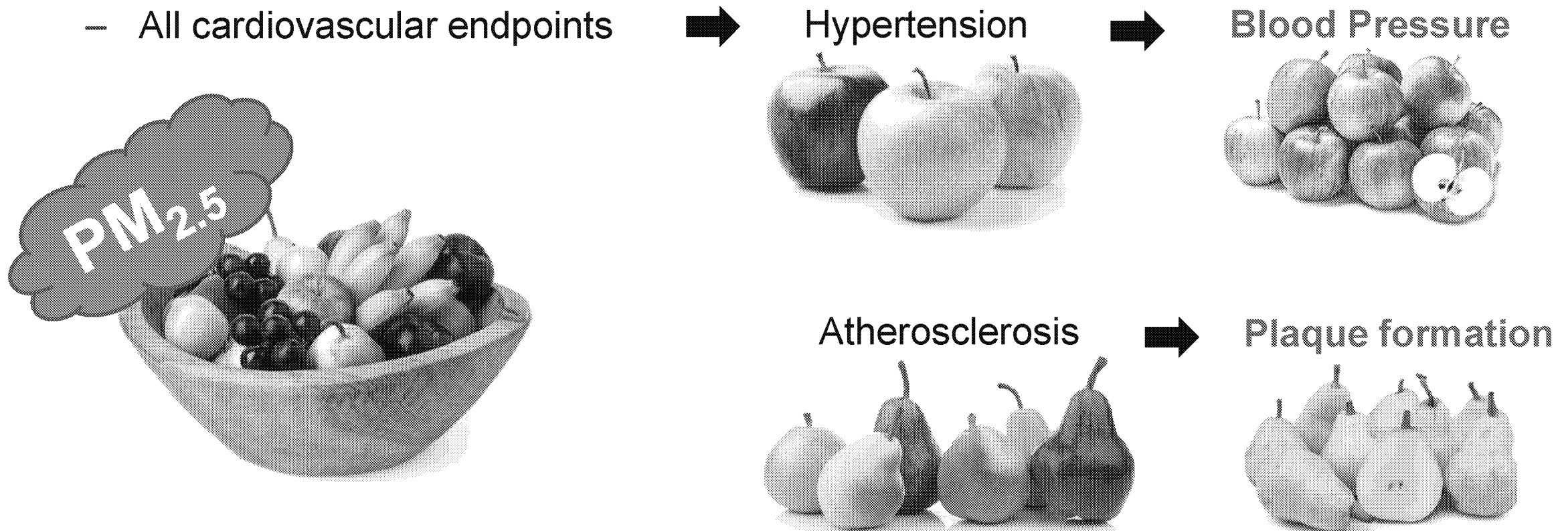
    Atherosclerosis ➡ Plaque formation

- **Is PM$_{2.5}$ associated with cardiovascular toxicity?**
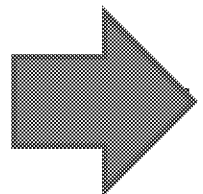
➡ Multiple health outcomes

– Single exposure

All cardiovascular endpoints ➡ Hypertension ➡ Blood Pressure
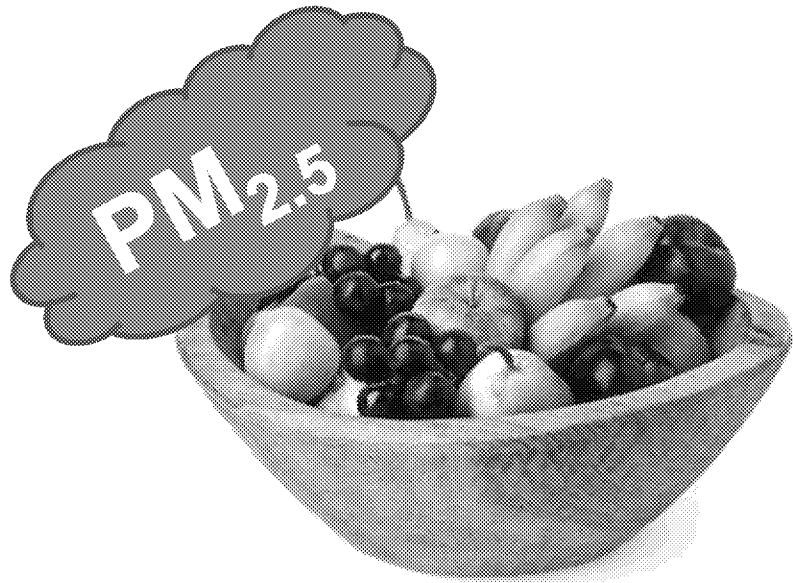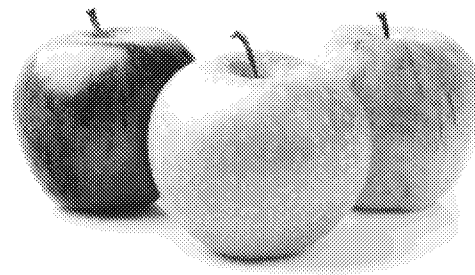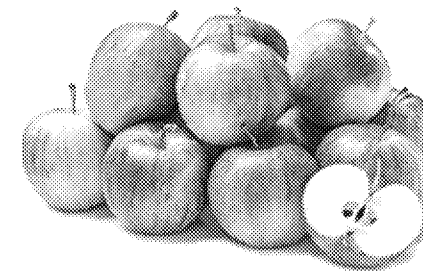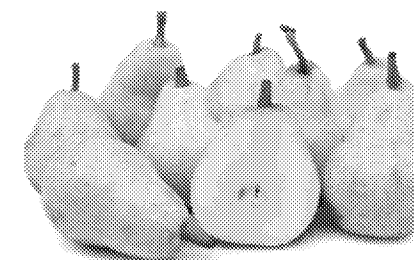
Atherosclerosis ➡ Plaque formation

- **Is Traffic-related Air Pollution associated with cardiovascular toxicity?**

  – Single or multiple health outcomes
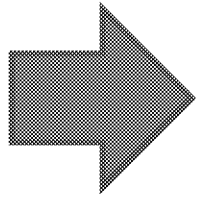
  ➡ Multiple exposures
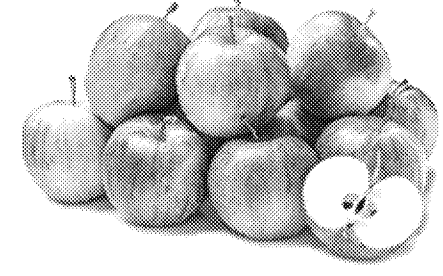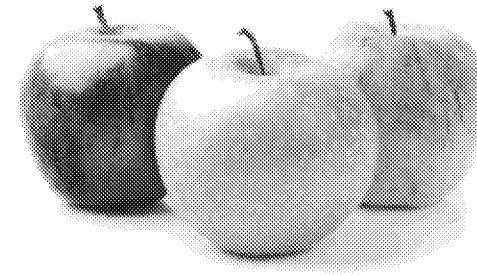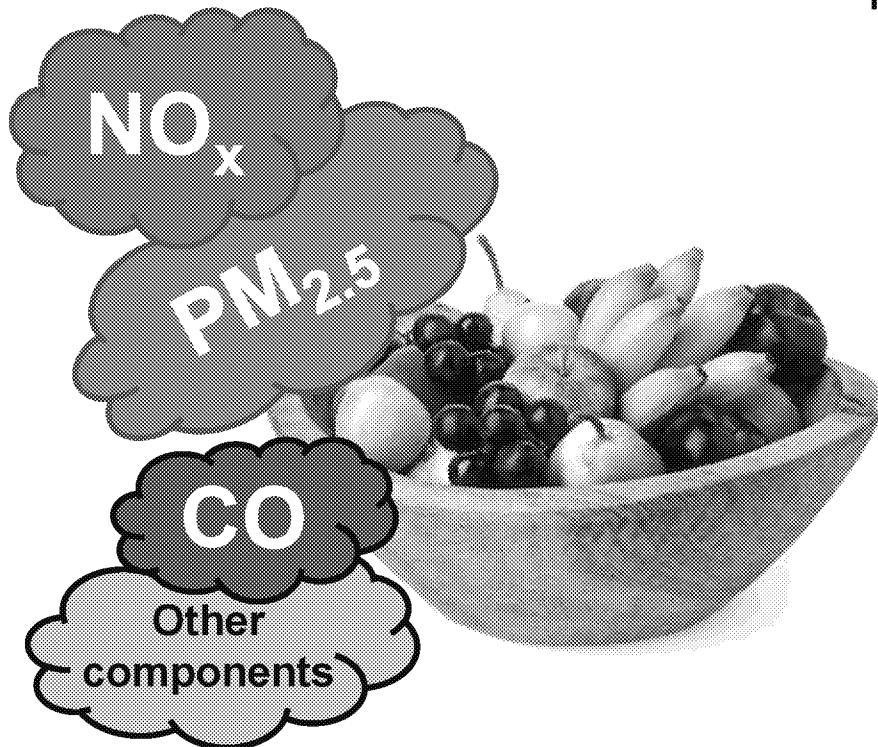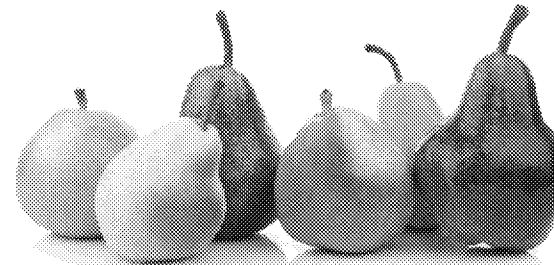
Evaluate evidence stepwise within exposure-outcome pairs

- Develop separate bodies of evidence
    - Exposure-outcome pairs ($PM_{2.5}$, other TRAP surrogates, direct traffic measures)
    - Assess individual study quality/risk of bias
    - Evaluate confidence in exposure-outcome pair bodies of evidence

- Synthesize across bodies of evidence
    - Re-evaluate confidence collectively and develop conclusions
    - Consider data on mechanism(s)
        - Overlapping/ independent?
    - Datasets
        - Overlapping or separate studies and populations?
        - Data or studies that control/adjust for other exposures?

Need for Case Examples on Multiple Exposures

- Examples?

- Options?

- Can we learn from read across?

- Can we learn from mixtures approaches?

- Stepwise approach for combined exposures
  - Flexibility within NTP's OHAT approach
  - TRAP and Hypertensive Disorders of Pregnancy

https://ntp.niehs.nih.gov/go/trap

Thank you
Questions?

Using Systematic Review and Meta-Analysis Methods to Inform Exposure Assessments

Jessica J. Frank*[1,2], Antonios G. Poulakos[3],

Rogelio Tornero-Velez[2], Jianping Xue[2]

Systematic Review in Exposure Science Summit
Arlington, Virginia
April 25, 2019

*Presenting Author, [1]Oak Ridge Institute for Science and Education and [2]National Exposure Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC 27709; [3]ASRC Federal Vistronix Contractor, U.S Environmental Protection Agency, Office of Research and Development, National Exposure Research Laboratory, Boston, MA 02109

Presentation Outline

➢ Research Context

➢ Article Identification Strategy

➢ Inclusion and Exclusion Criteria

➢ Screening Flow

➢ Exclusions Based on Quality Considerations

➢ Meta-analysis Methods

➢ Example to Illustrate the Robustness of the Generated Data

➢ Example of Meta-analysis Results

Water

Soil

Dust

Food

Air

Pb

How do the literature data compare to available national survey data?

Are there robust data in the literature that can provide a broader picture of environmental Pb contamination to support exposure modeling?

Inclusion & Exclusion Criteria

General Inclusion Criteria

➤ Reference is written in English

➤ Published between the years 1996 – 2016

➤ Reference is a peer-reviewed or grey article

➤ Study site or population is within the United States

➤ Pb is measured in one of the following environmental media: air, soil, water, dust, food, and blood

➤ Necessary summary statistics are clearly reported

➤ No duplication of data part of national surveys used in the study

Media-Specific Inclusion Criteria

➤ Soil samples are collected within the top 30 cm layer, with a range up to 50 cm

➤ Samples associated with aquatic environments are from fresh water environments, except in the case of food

➤ Baseline values are used from intervention or remediation studies

➤ Data duplicated across studies: select the most robust, or most recently and clearly described.
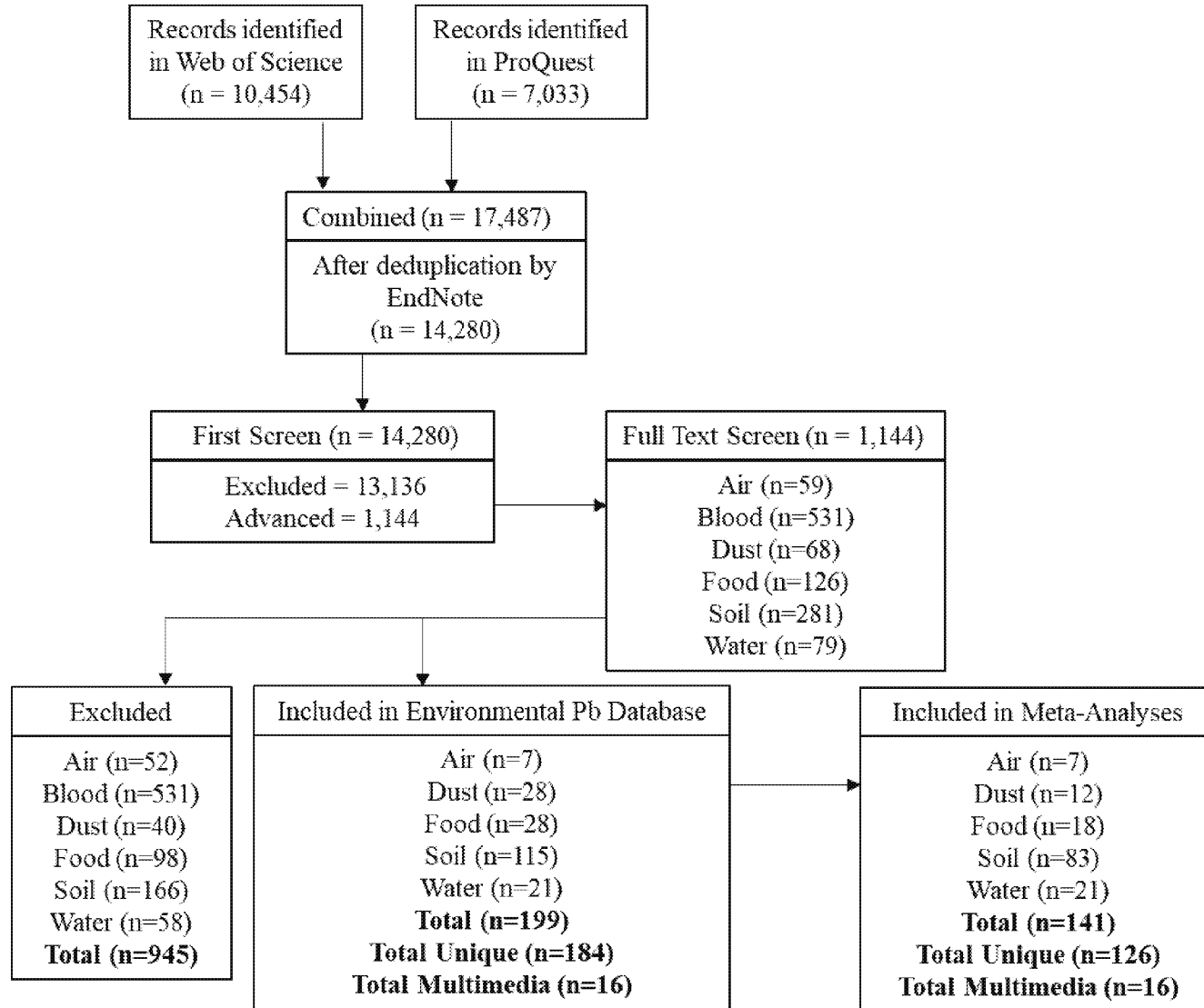
> Two screening phases

> Two researchers independently screened articles

> Two researchers reviewed database

> Multiple database reviews

> Meta-analyses are subset of data

Quality Considerations

➤ Two articles meeting IE criteria removed due to quality considerations

Study 1:
  ➤ Concerns with limits of detection being too high (10 ppm)
  ➤ More than half of samples below LOD

Study 2:
  ➤ Samples analyzed by undergraduate class of 45 students
  ➤ Incongruent raw data and statistics
  ➤ Community garden in Superfund designated area

➢ Random-effects model:

- Heterogenous distribution of contamination
- Samples approximate multiple true statistical populations
- Accounts for between-study variation and random error

➢ Single group summary *not* effect size

➢ Written in SAS and verified using example data and problem sets from Borenstein et al.

Michael Borenstein
Larry V. Hedges
Julian P. T. Higgins
Hannah R. Rothstein

Introduction to
Meta-Analysis

WILEY
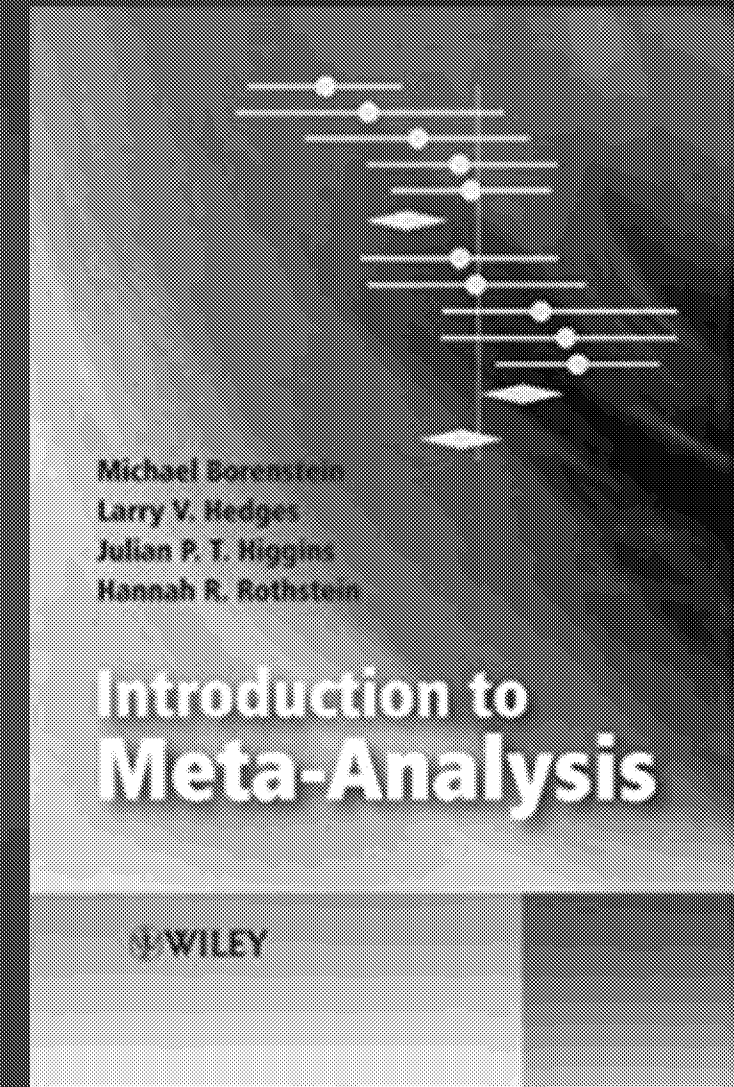
Example of Data Robustness

Groundwater
Drinking Water
Surface Water

Water

Dust Loading
Dust Concentration
SF Dust

Residential
Recreational
SF Soils

Soil

Dust

Air

Wild-caught
Produce
Livestock
SF Wild-caught

Food

Indoor
Outdoor

Residential Soil Pb, Non-Superfund (ppm)		
Single Group Summary	Sample Size	Mean (SE)
Literature Data Only		
Non-Urbanized Area Residential Sites	284	219 (36)
Urbanized Area Residential Sites	7440	629 (32)
Combined Residential Sites	8926	526 (26)
Literature and National Survey Data		
Non-Urbanized Area Residential Sites	473	153 (20)
Urbanized Area Residential Sites	8861	610 (31)
Combined Residential Sites	15044	451 (19)

Soil Pb ppm
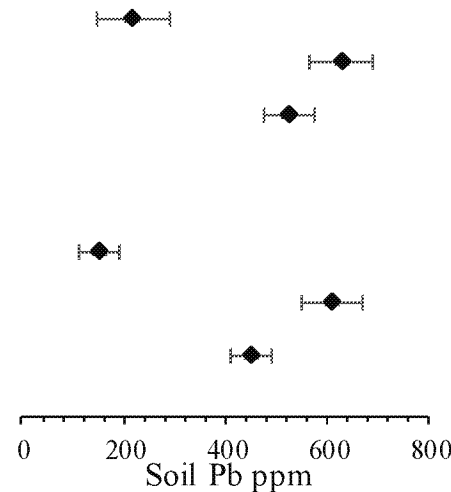
➢ Urbanized areas ~3x non-urbanized areas

➢ HUD surveys [Pb] are similar to non-urbanized areas from literature, Elless study is similar to combined literature data

➢ HUD NSLAH: n=3566, *M(SE)*= 219(10)
➢ HUD AHHA: n=942, *M(SE)*= 160(16)
➢ USGS Geochemical Survey: n=4841, *M(SE)*= 26(3)
➢ Elless et al. (2008): n=1400, *M(SE)*= 525(32)

Recreation Related Soil Pb, Non-Superfund (ppm)

Single Group Summary	Sample Size	Mean (SE)
Literature Data Only		
Benchmark	93	11 (2)
Associated to Freshwater	595	63 (2)
Forests and Open Space	1828	77 (2)
Schoolyards and Playgrounds	182	87 (9)
Roadside	1048	115 (10)
Community and Residential Gardens	2082	293 (33)
Outdoor Shooting Ranges	563	3604 (55)
Literature and National Survey Data		
Forests and Open Space	4843	76 (2)

Soil Pb ppm (1, 10, 100, 1000, 10000)
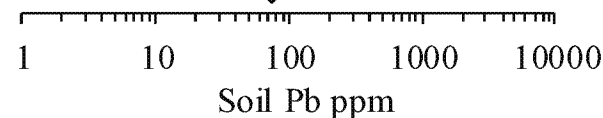
- Literature data available but limited national survey data for these subgroups.

- Some observations:
  - Literature values for forests and open space similar to USGS national survey
  - Community gardens appear at the higher end of the range
  - Data for shooting ranges likely an outlier for recreation related soil Pb measurements

Water

Soil

Dust

Food

Pb 82

Air

Frank.Jessica@epa.gov
919-541-4040

References

Borenstein, M., Hedges, L. V., Higgins, J. P., & Rothstein, H. R. (2011). *Introduction to meta-analysis*. John Wiley & Sons.

Elless, M. P., Ferguson, B. W., Bray, C. A., Patch, S., Mielke, H., & Blaylock, M. J. (2008). Collateral benefits and hidden hazards of soil arsenic during abatement assessment of residential lead hazards. Environmental pollution, 156(1), 20-28.

U.S. Environmental Protection Agency (2014). *Technical Review Workgroup Recommendations Regarding Gardening and Reducing Exposure to Lead-Contaminated Soils*. U.S. Environmental Protection Agency, Washington, DC, OSWER 9200.2-142, 2014. Retrieved from https://semspub.epa.gov/work/HQ/174577.pdf

Systematic Review for Updating the PCB Exposure Estimation Tool

Linda Phillips, EPA/ORD/NCEA

April 25, 2019

PCB Exposure Estimation Tool

Background:

- Developed Tool in 2009 to estimate PCB exposure from school and non-school pathways
- Calculates the maximum school indoor air PCB concentrations (ng/m^3) that do not exceed the RfD, considering other background exposures
- Uses average background concentrations for dust, soil, air based on data from the scientific literature
- Bases dietary intake of PCBs on FDA Total Diet Study Data

234

Systematic Review to Update Tool

Current Efforts to Update Tool:
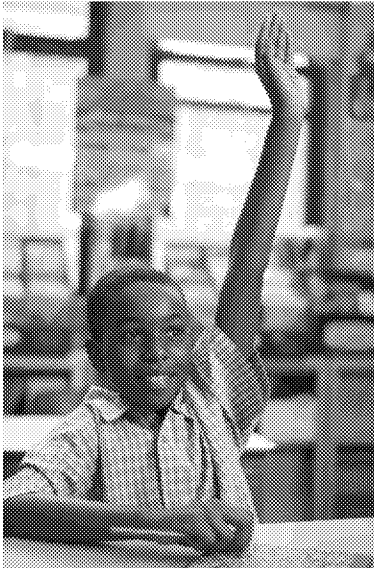
- Conducting <u>systematic review</u> to identify relevant literature on
  - background media concentrations of PCBs in:
    - soil
    - dust
    - indoor air
    - outdoor air
  - dietary exposure

Systematic Review to Update Tool

Process:

- Developed PECO statement and search terms
- Conducted literature search and citation mapping
  (EPA HERO Library Staff)
- Screened titles/abstracts using DistillerSR
- Reviewed full text of selected papers
- Summarized and evaluated papers based on General Assessment Factors
- Compiled data for updating Tool

236
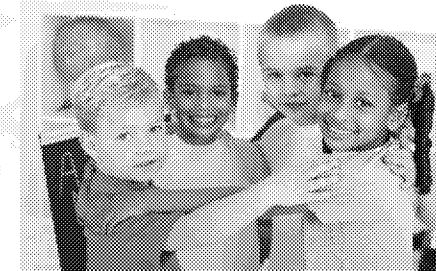
Systematic Review to Update Tool

PECO:

- Background levels of PCBs in environmental media
- Dietary exposure to PCBs
- Representative of school age children and adults
- US data
  - data from other countries for comparative purposes only
- Nationally representative
  - site-specific background (reference) in the absence of national data
- Total PCBs defined as total congeners, homologue groups, or Aroclors

Systematic Review to Update Tool

Literature Search:

- Keywords:
  - Polychlorinated biphenyls or PCBs, or related terms
  - Concentration or levels
  - Soil or soil ingestion
  - Dust or dust ingestion or dust contact or dust dermal
  - Air or inhalation (indoor, outdoor, ambient)
- Exclusions:
  - Emissions or emissions modeling
  - Physical-chemical properties
  - Sources
  - Fate
  - Wildlife
  - Toxicity

238

Systematic Review to Update Tool

Literature Search:

- PubMed
- Web of Science
- ToxLine
- Citation Mapping (using papers cited in original Tool)

239

Total = 3,046 (after duplicates removed)

| PubMed (n=897) | WOS (n=2,174) | ToxLine (n=50) | Citation Mapping (n=624) |

TITLE AND ABSTRACT SCREENING

Screened
3,046 titles/abstracts

Excluded
2,814 records not relevant to PECO

FULL TEXT REVIEW

Reviewed
232 full text records

Excluded
164 records based on GAFs

Studies Considered further (n=68)
34 soil studies; 9 dust studies;
11 indoor air; 26 outdoor air
2 dietary

240

Systematic Review to Update Tool

Title and Abstract Screening:

- Distiller SR (3,046 papers)
- 2 Screeners
- Tagged for relevance
    - Yes
    - Yes, but already in Tool
    - No
    - Unclear
- Tagged by topic
    - Dust
    - Soil
    - Indoor Air
    - Outdoor Air
    - Dietary

Reference Label(s):

Add Labels here

The occurrence of five groups of semivolatile organic compounds (SVOCs) (total of ~120 distinct chemicals) was investigated in senior care facilities in the United States and in Portugal. Indoor settled dust samples were collected from fourteen facilities, and the concentrations of organophosphate esters (OPEs), brominated flame retardants (BFRs), polycyclic aromatic hydrocarbons (PAHs), organochlorine pesticides (OCPs), and polychlorinated biphenyls (PCBs) were measured in these samples. Overall, OPEs, PAHs, and BFRs were the most abundant, and OCPs and PCBs were the least abundant SVOC groups in dust collected from both U.S. and Portuguese facilities. $\sum$OPE, $\sum$PAH, and $\sum$BFR concentrations were significantly higher in U.S. facilities than those in Portuguese facilities (P < 0.001), while $\sum$OCP and $\sum$PCB concentrations were not different between the two countries (P < 0.05). The samples were collected from three different microenvironments, including bedrooms, living rooms, and corridors. $\sum$OPE, $\sum$PAH, and $\sum$BFR concentrations were up to five times higher in corridors compared to bedrooms and living rooms. $\sum$OCP and $\sum$PCB concentrations were overall higher in bedrooms and in living rooms and lower in corridors.

Submit Form and go to | This Form - Next Reference

Source ○ Literature search ● Citation mapping   Clear R

Does the study meet the PECO criteria?

● Yes ○ Yes, but already cited in the tool ○ No

○ Tag as potentially relevant supplemental material

Exposure type?

☑ Dust ☐ Soil ☐ Indoor Air ☐ Outdoor Air ☐ Dietary

242

Systematic Review to Update Tool

Full Text Review and Summary (232 papers):

HERO ID and Citation	Dust	Soil	Indoor Air	Outdoor Air	Dietary	Include?			Why or why not?	Primary GAF if 'No'	Summary
						Yes	No	Other			
RefID 2150856 A. Martinez, N. R. Erdman, Z. L. Rodenburg, P. M. Eastling, K. C. Hornbuckle. Spatial distribution of chlordanes and PCB congeners in soil in Cedar Rapids, Iowa, USA. Environmental Pollution. 2012. 161:222-228 https://heronet.epa.gov/heronet/index.cfm/reference/download/reference_id/2150856		Soil				Yes			Data for U.S. background location; multiple congeners measured	--	Residential soils (n=64) from Cedar Rapids, Iowa, were collected and analyzed for PCBs; total PCB concentrations (sum of 164 congener peaks) ranged from 0.003 to 1.2 ug/g dw; mean = 0.056 ± 0.160 ug/g dw; median = 0.020 ug/g
RefID 2150858 X. Zheng, X. Liu, G. Jiang, Y. Wang, Q. Zhang, Y. Cai, Z. Cong. Distribution of PCBs and PBDEs in soils along the altitudinal gradients of Balang Mountain, the east edge of the Tibetan Plateau. Environmental Pollution. 2012. 161:101-106 https://heronet.epa.gov/heronet/index.cfm/reference/download/reference_id/2150858		Soil					No		Remote location	Applicability and Utility	Soil samples collected from 7 sites on Balang mountain range, Tibet (far from residential sites); analyzed for 25 PCB congeners; range of sum of 25 congeners = 0.000059 to 0.000287 ug/g) mean = 0.000163 ug/g
RefID 2150973 K. Mishra, R. C. Sharma, S. Kumar. Contamination											

Systematic Review to Update Tool

General Assessment Factors

- **Soundness** - measures, methods or models are reasonable for, and consistent with, the intended application.

- **Applicability and Utility** - information is relevant for the Agency's intended use.

- **Clarity and Completeness** - clarity and completeness of data, assumptions, methods, quality assurance, etc.

- **Uncertainty and Variability** - variability and uncertainty are evaluated and characterized.

- **Evaluation and Review** - independent verification, validation and peer review.

U.S. Environmental Protection Agency (2003) A summary of general assessment factors for evaluating the quality of scientific and technical information. Science Policy Council, Washington, DC. EPA/100/B-03/001. Available online at: https://www.epa.gov/risk/summary-general-assessment-factors-evaluating-quality-scientific-and-technical-information.

Systematic Review to Update Tool

Compile and Summarize Data:

INDOOR AIR SUMMARY						Results	
Study	Include?	Location	Site	N	Congeners	Central	Range
Ampleman et al., 2015	Yes	Indiana	homes	--	201	geometric mean ± SE = 1.0 ± 0.02 ng/m3	--
		Iowa	homes	'--		geometric mean ± SE = 0.44 ± 0.1 ng/m3	'--
		Indiana	schools	13		geometric mean ± SE = 6.4 ± 0.1 ng/m3	'--
		Iowa	schools	11		geometric mean ± SE = 8.4 ± 0.4 ng/m3	'--
Marek et al., 2017	Yes	Indiana, Iowa	schools	2 urban, 4 rural	209	--	0.5 to 194 ng/m3
Fitzgerald et al., 2011	Yes	New York	homes in study and reference area	176	Aroclors 1242, 1254, and 1260	mean = 14 ng/m3	0.6 to 233 ng/m3
Harrad et al., 2009	Already in Tool	Canada	homes	10	congeners with 3-7 chlorines	mean = 6.9 ng/m3	1.1 to 14.4 ng/m3
Currado and Harrad, 199	Already in Tool	England	laboratories, offices, homes	14	tr- through hepta-chlorianted	mean = 9 ng/m3	1.1 to 69 ng/m3
Takigami et al., 2009	Supplemental	Japan	homes	4	mono- through deca chlorinated	--	0.73-1.5 ng/m3
Menichini et al., 2007	Supplemental	Italy	homes	3	62	--	6.5 to 33 ng/m3
Bohlin et al., 2008	Supplemental	Mexico, urban	homes	35	43	mean = 0.47 ng/m3	0.21 to 0.84 ng/m3
		Mexico, semi-urban	homes			mean = 0.19 ng/m3	0.1 to 0.32 ng/m3
		Sweden	homes			mean = 0.89 ng/m3	0.33 to 1.6 ng/m3
		UK	homes			mean = 0.86 ng/m3)	0.15 to 2.1 ng/m3
Harrad et al., 2006	Supplemental	England	homes	31	total PCBs = 5 x sum of 6 congeners	mean= 2.8 ng/m3	0.487 to 9.764 ng/m3
			offices	33		mean = 18.1 ng/m3	0.816 to 101.8 ng/m3
			public microenvironments	3		mean = 30.7 ng/m3	1.08 to 81.5 ng/m3
Zhang et al., 2011	Supplemental	Canada	homes, offices, laboratories	20	total PCBs = 5 x sum of 6 congeners	geometric mean = 6.5 ng/m3	0.8 to 130.5 ng/m3
Frederiksen et al., 2012	Supplemental	Denmark	apartments	20	total PCBs = 5 x sum of 6 congeners	mean = 6.03 ng/m3	<LOQ to 30.6 ng/m3
Number of Studies	11 Total: 3 Yes, 2 Already in Tool, 6 Supplemental						
AVERAGE YES (US only) (ng/m3)						6.0	0.5 to 233
AVERAGE ALL (ng/m3)						7.0	<LOQ to 233
Value in Current PCB Exposure Estimation Tool (ng/m3)						6.9	

Systematic Review to Update Tool
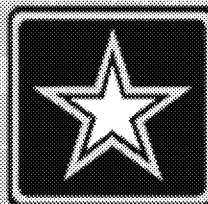
Next Steps:

- Update Tool and Documentation
- Peer Review
- Respond to Comments
- Release New version of Tool

Thank you for your attention!

Contact Information
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202-564-8252; phillips.linda@epa.gov

Systematic Review and the Department of Defense

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Environmental Laboratory,
US Army Engineer Research and Development Center

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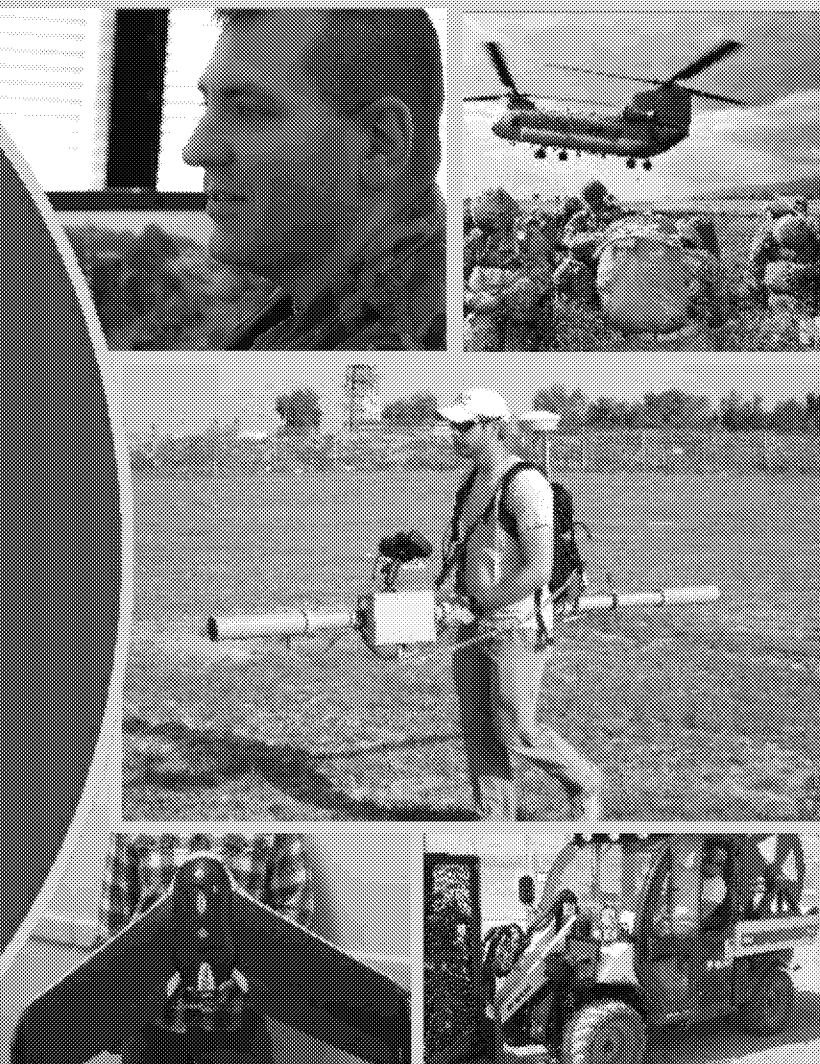
Systematic Review in Exposure Science Summit, April 25, 2019

ERDC

US Army Corps of Engineers

DISCOVER | DEVELOP | DELIVER

Relevance and importance of Summit to DoD

Exposure is a major concern for DoD.

- Large number of Soldiers and civilians in many different situations

- DoD total active and armed forces = ~2 Million and nearly 800 military bases in more than 70 countries and territories abroad

- Soldiers exposed to a wide range of chemicals during active duty

- DoD spends >$50 billion/year in health care for service members, retirees, and their families

- High cost as a result of exposure: e.g. due to potential exposure of soldiers and civilians to as a result of DoD activities, the DoD is facing >$2 billion remediation/management costs for PFASs at military bases and other sites.

- DoD can lose use of critical technologies if linkage of exposure to effects is faulty

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Relevance and importance of Summit to DoD

- USACE civil works activities (dredging, construction, land/habitat management) must manage contaminated sediments to minimize exposure effects.
- Understanding exposure directly impacts mitigation and clean up efforts in DoD.
- Knowing and understanding how warfighters and civilians may be exposed, as well as knowing and understanding the routes of exposure for plants and wildlife on the civil works side are critical.

We need a way to systematically bring together the literature in a transparent way for us to better understand exposure. This includes making sure we get all of the available information gathered, screening it to find the right papers, and re-analyzing the data to ensure we understand the likely exposure due to various routes and the uncertainty in those measures.

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Collaboration opportunities

- DoD relies on S&T and programs developed in other federal agencies to complement work done in the DoD

- Several ongoing investigations into emerging contaminants of concern and how soldiers are exposed to different chemicals provide areas of collaboration

- PFAS provides us an opportunity to work together across the Federal family.

- What can we understand about the PFAS chemicals that have been well studied?

- What can we say about how well knowledge about PFOS and PFOA exposures might also inform us about the other PFAS chemicals?

- How can we come together to better understand the environmental fate and transport, point-source pollution, and non-point-source pollution?

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Why it's important to invest time in this Summit professionally

- It is clear that systematic review principles can be used to address hypotheses we have about chemicals.

- Can we also use it to identify knowledge gaps and to prioritize future research?

- If so, how might we do that?

- Investing time here helps ensure that regulatory agencies and agencies affected by regulations have a common frame of reference and can interact together.

- There is a critical need for transparency and accessibility, and understanding other agencies' tools, approaches, results

US Army Corps of Engineers • Engineer Research and Development Center

Challenges in communication and coordination across agencies

- Different priorities and end users/customers can result in DoD being uninformed about information form regulatory agencies
- E.g. release of information or findings before DoD can develop a response
- How do we do a better job of communicating and collaborating?
- We all have different IT requirements about what we can and can't use.
- For instance, FDA and DoD cannot use Box or Dropbox to share files with other Agencies that do have that ability.
- Most federal agencies have access to MAX.GOV -- is that an option to share?
- What are the downsides of using MAX.GOV?
- Are there other solutions to help us better collaborate together?
- Are there mechanisms by which we can better align our research strategies?

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Thanks

US Army Corps of Engineers • Engineer Research and Development Center

File Name

The Promise of Automation and Machine Learning

in Systematic Reviews

Vickie Walker

National Toxicology Program

US National Institute of environmental Health Sciences

April 25, 2019

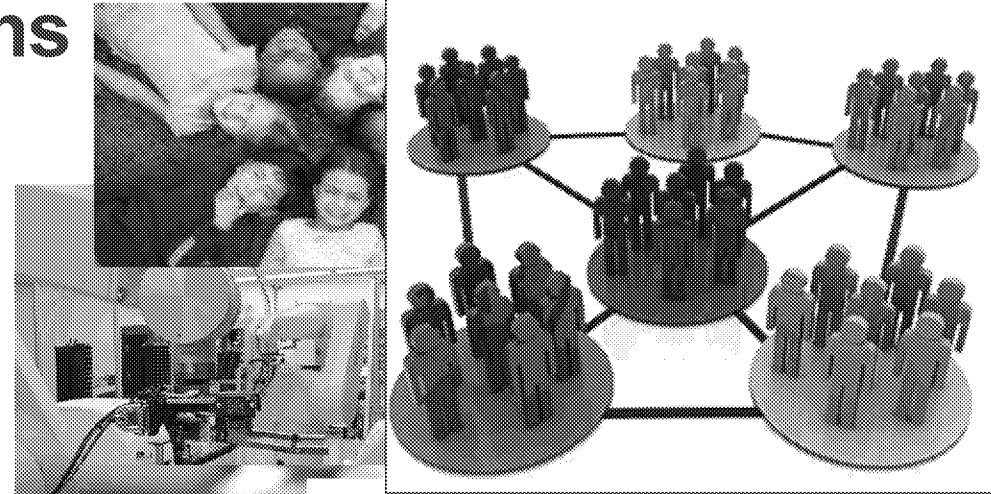**Systematic Review In Exposure Science Summit**

Applying SR to Environmental Questions

- **Growing Experience in Applying SR**
  - SR methods to integrate evidence from human, animal, and mechanistic studies

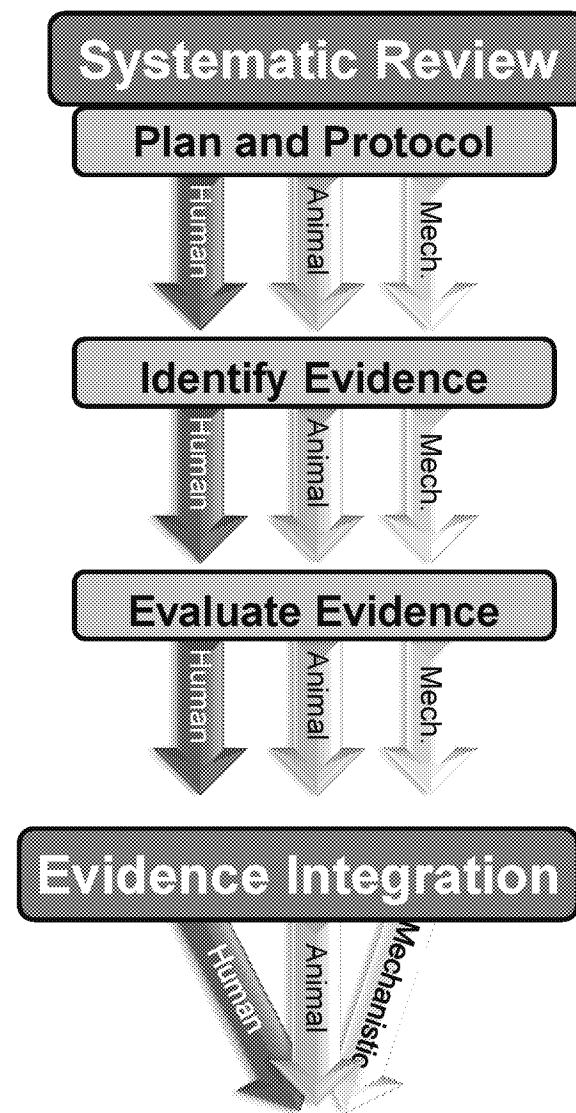Exposure Biology at NIEHS

- **Challenges**
  - Integrate evidence from new approach methodologies
  - Consider collections of environmental exposures rather than single events
  - Find and translate "evidence" despite volume of research
    - 3 science articles published per minute
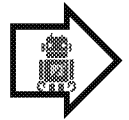   - 2 million+ research publications per year

Where in SR Are We Best Positioned for Automation?

SWIFT-ACTIVESCREENER

DistillerSR

SYSTEMATIC Review Facility

Systematic Review

Plan and Protocol

Human | Animal | Mech.

Identify Evidence

Human | Animal | Mech.

Evaluate Evidence

Human | Animal | Mech.

Evidence Integration

Human | Animal | Mechanistic

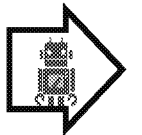# Where in SR Are We Best Positioned for Automation

Problem Formulation

- Outline opportunities for automated/ semi-automated approaches
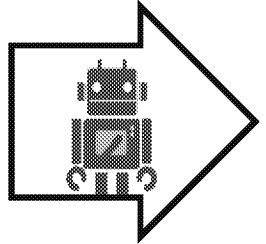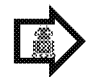
Identify

- Literature searching
- Selection of relevant studies
- Data extraction
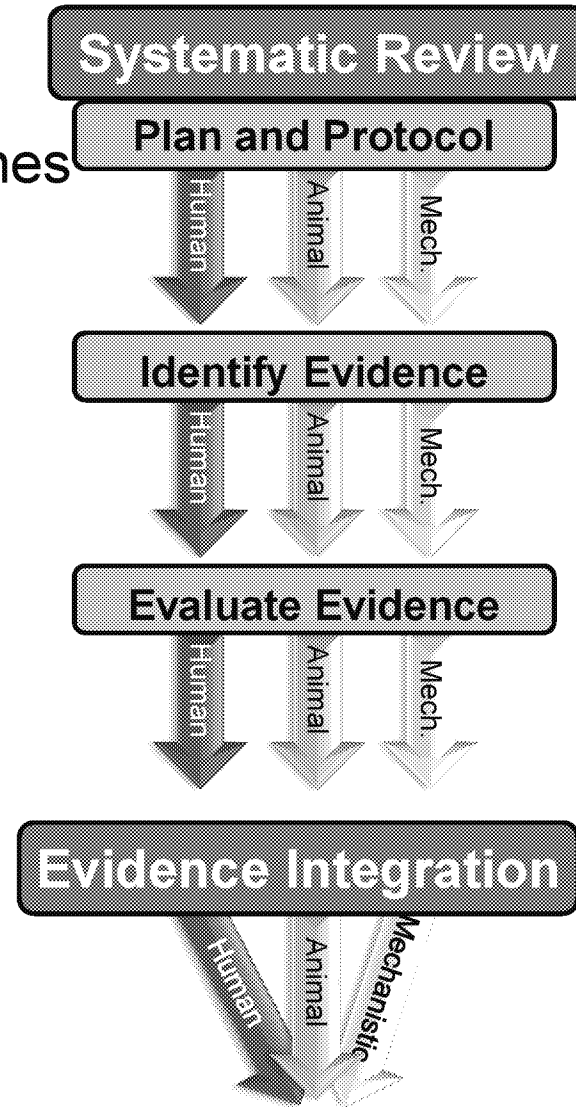- *Multiple applications, case studies, research efforts*

Evaluate

- Critical Assessment (Quality and Applicability)
- *Emerging area for research and case studies*

Evidence Integration

- *What will it take to support and trust full AI decision making?*

Systematic Review

Plan and Protocol

Human | Animal | Mech

Identify Evidence

Human | Animal | Mech

Evaluate Evidence

Human | Animal | Mech

Evidence Integration

Human | Animal | Mechanistic

Thank you
Questions?